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San Francisco, June 18-22, 1958

VOLUME XXXIII

NUMBER 2

# **DISEASES**

*of the*

# **CHEST**

OFFICIAL PUBLICATION



PUBLISHED MONTHLY

Brotherhood Week—February 18-23  
For Peace and Freedom

FEBRUARY  
1958

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**Fifth International Congress on Diseases of the Chest**  
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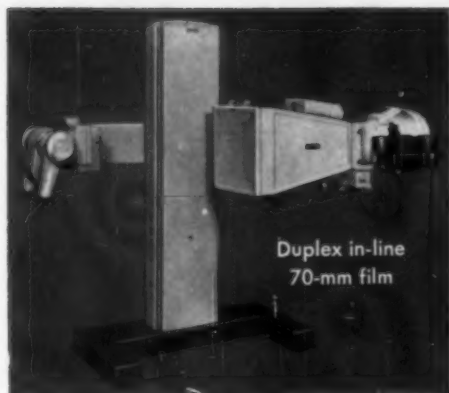
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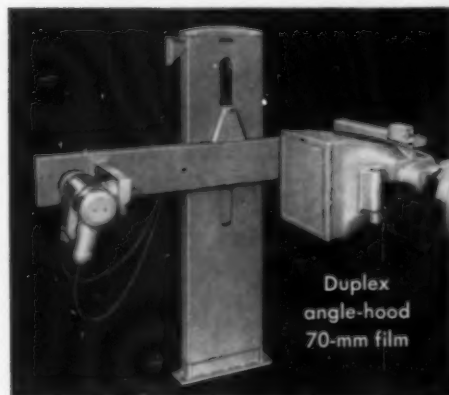
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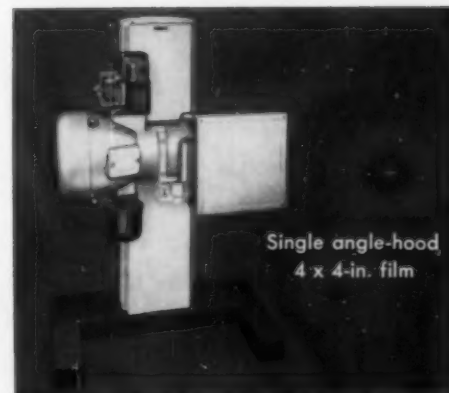


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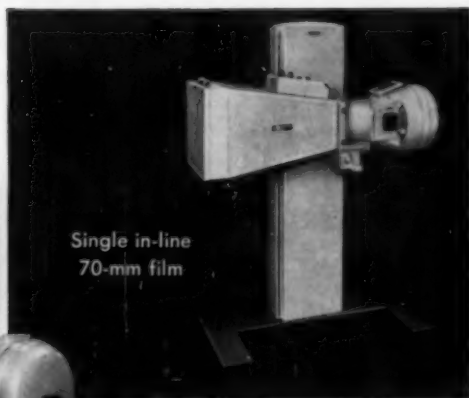
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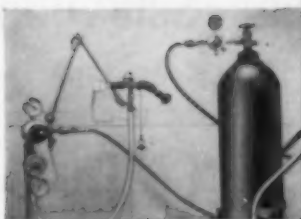
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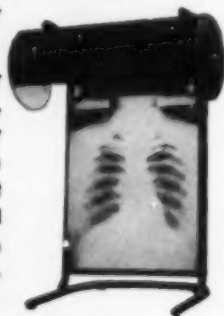
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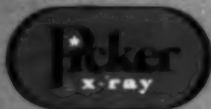
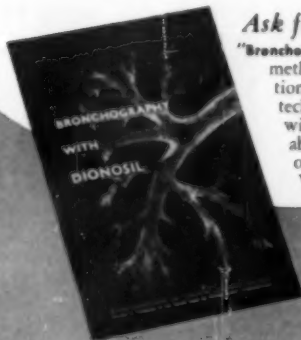
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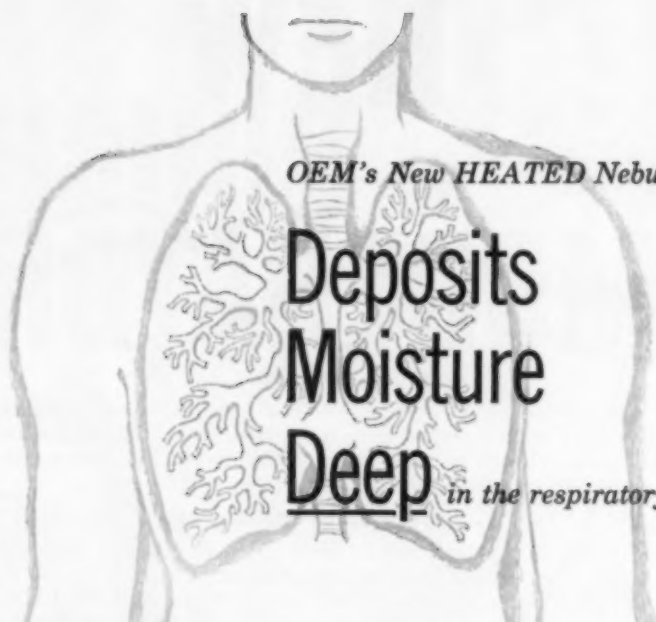
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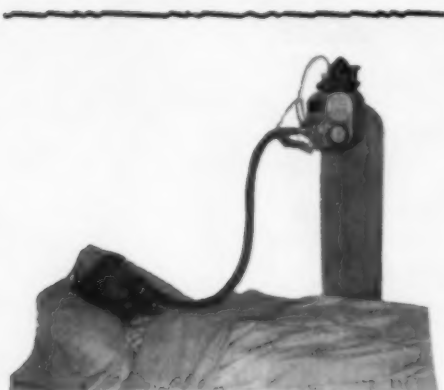
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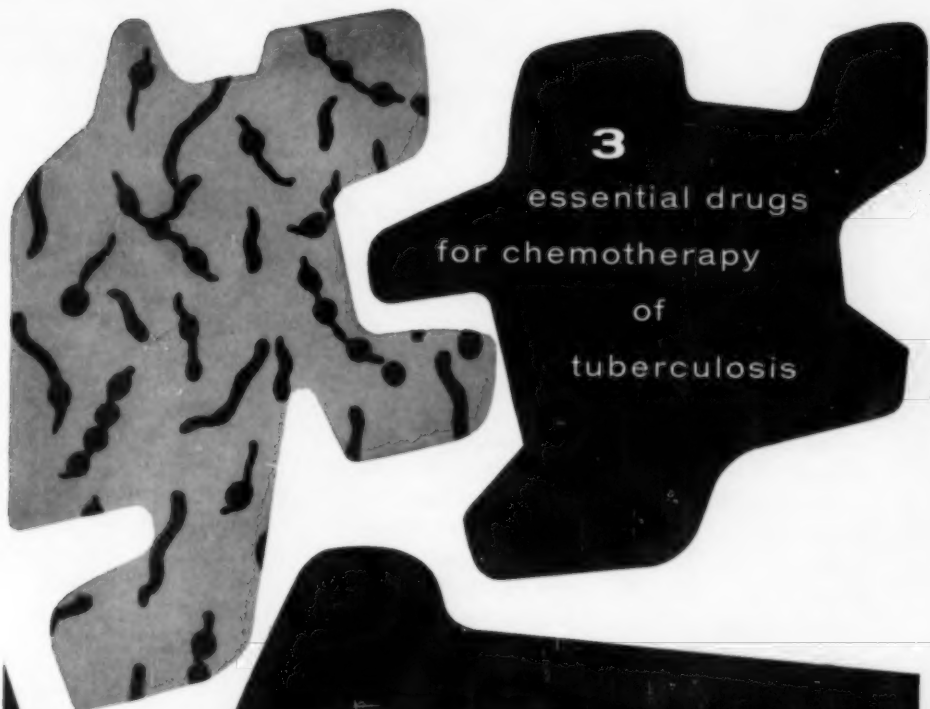
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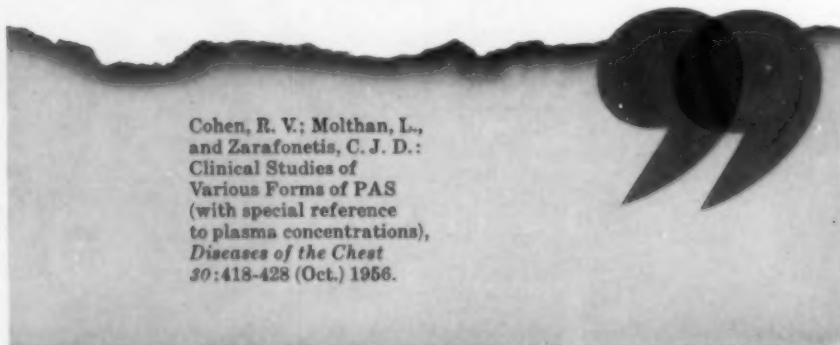
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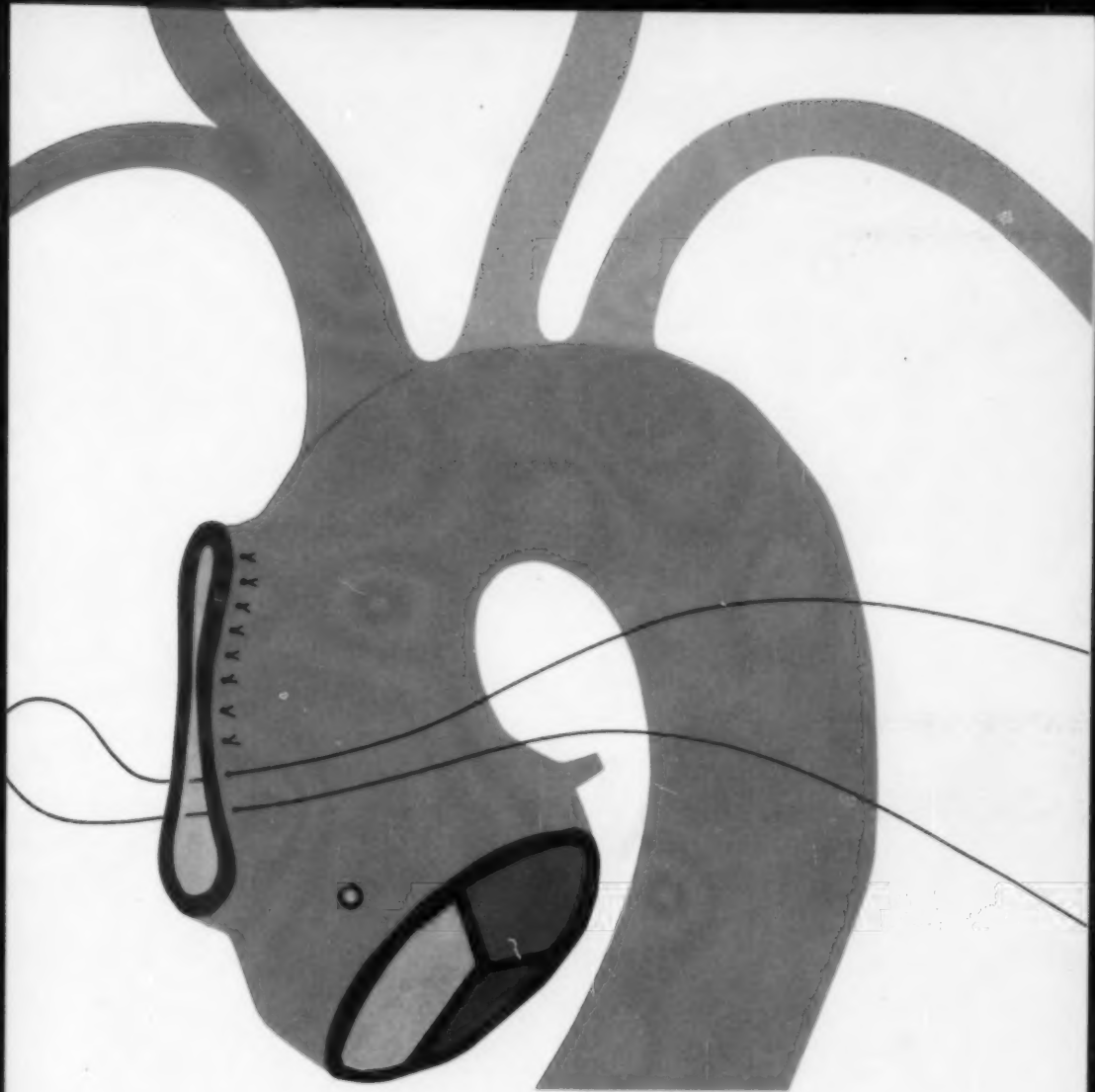


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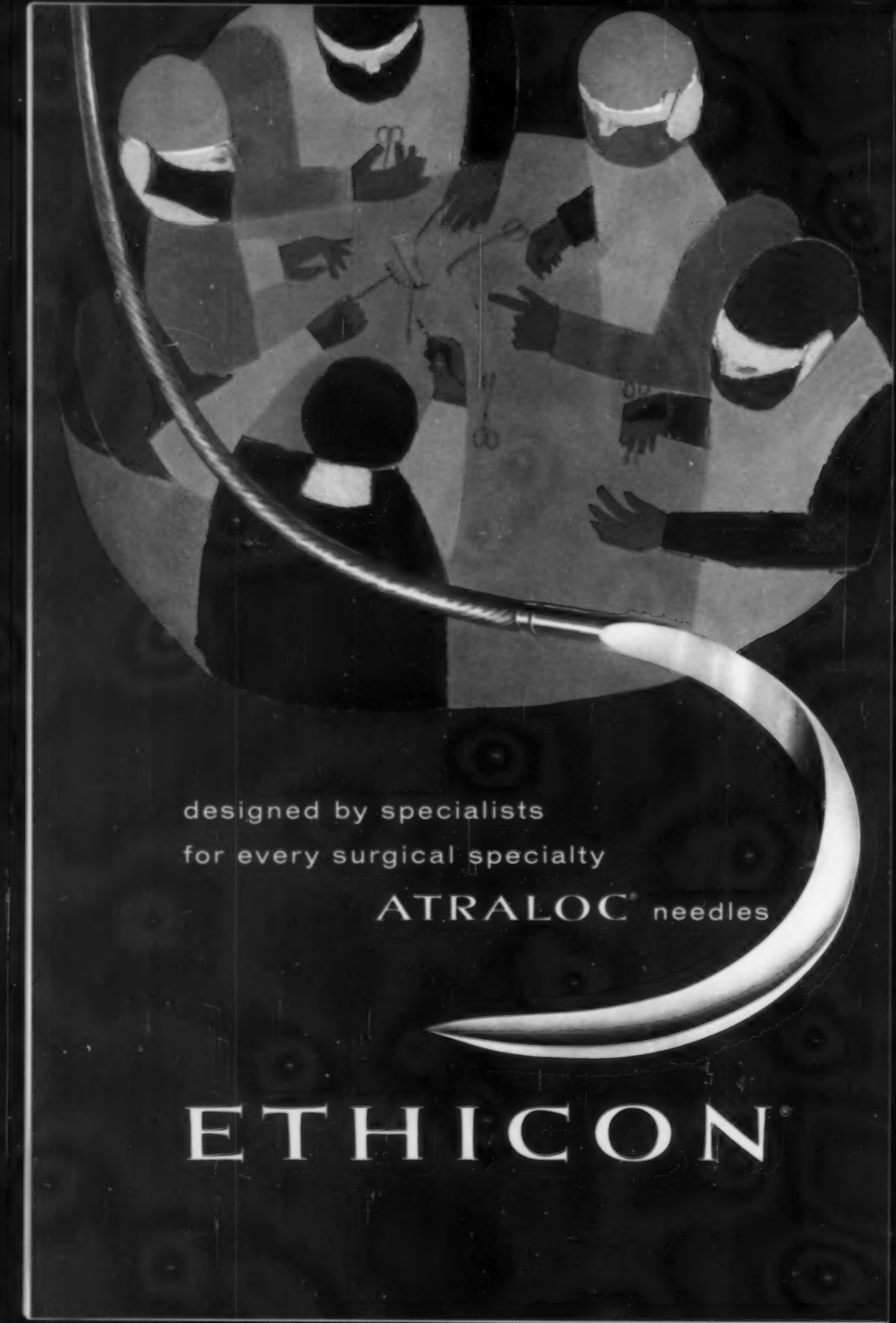
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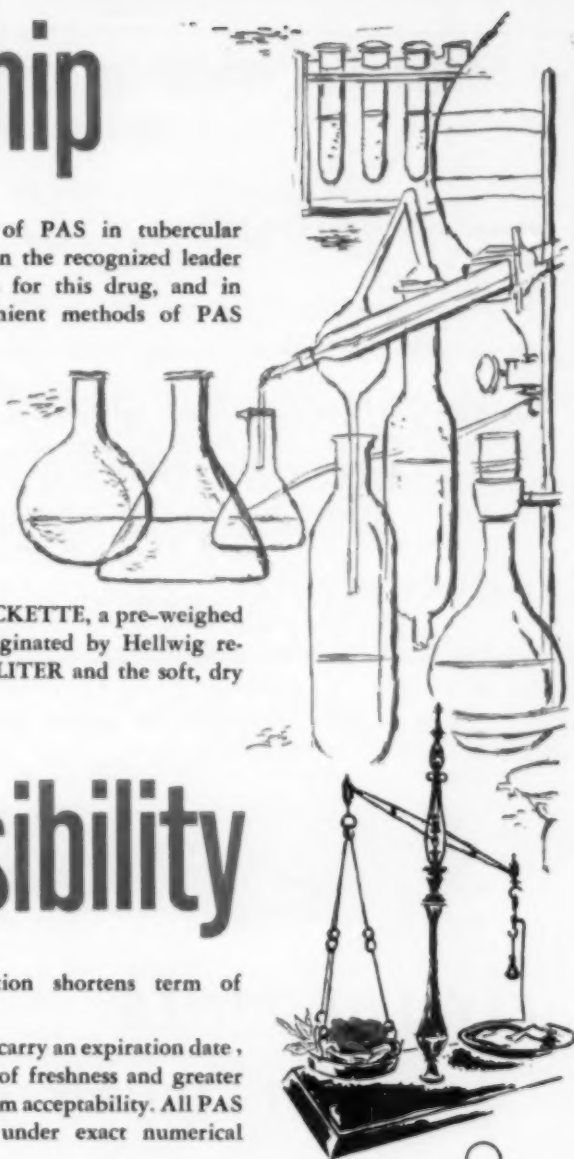
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2. Berk, Gordon J., New York: A New Office for Medical and Industrial Research, Aerosols, Clinical and Pharmacological Effects, personal communication, July, 1957.

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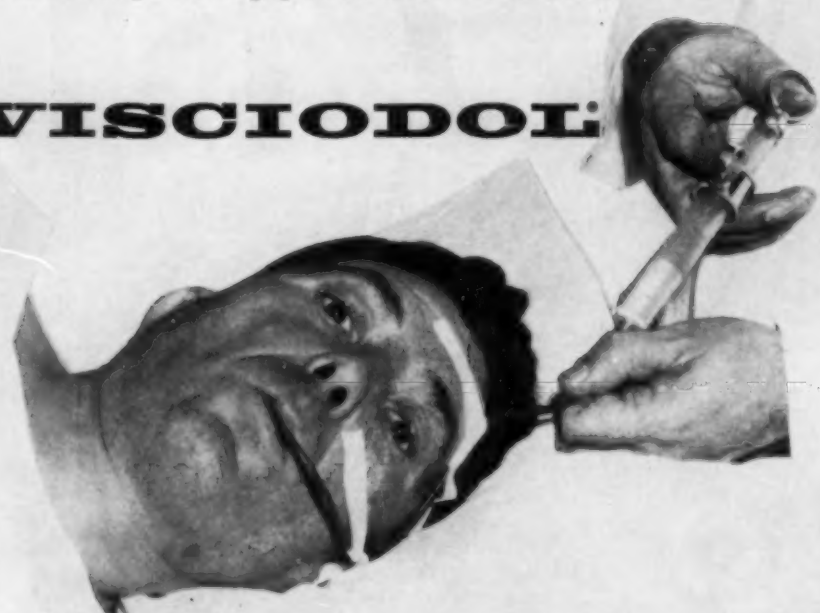
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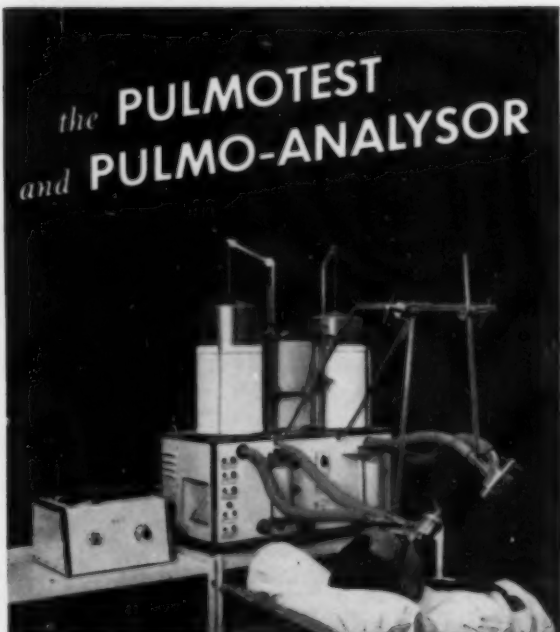
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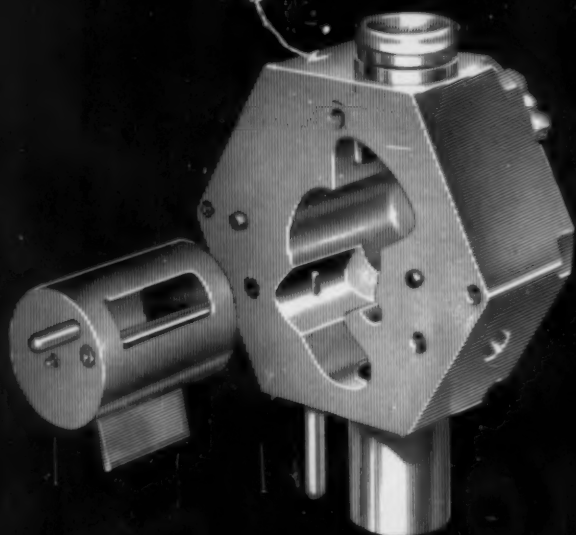
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# DISEASES of the CHEST

VOLUME XXXIII

FEBRUARY, 1958

NUMBER 2

## Inhalation Hazards in Nuclear Energy Programs\*

### Stable Elements

G. W. H. SCHEPERS, M.D., D.Sc., F.C.C.P.\*\*

Saranac Lake, New York

The continuing, far from dispassionate, public debate over the effects of nuclear tests on the health of future generations of mankind has fortunately focused attention on the need for control of a potential man-made environmental hazard probably even before it has become a reality. The current program of atom and hydrogen bomb manufacture will perhaps only be terminated when one of the militant human factions stumbles onto a yet more effective, if not more dreadful, method of subduing its adversaries or when extra terrestrial adventures pre-empt the unified resources of all mankind. We may as well attempt meanwhile to discover how to live with the bombs. This will only become possible if we recognize all the possible modes of exposure, have precise knowledge about the nature of the injury to be anticipated, and understand what the permissible toxicity tolerances will be.

For the present the major concern is over the effects of radiation, and most emphasis is placed on the hazard associated with radioactive "fall-out" following thermonuclear detonations. It will be a pity if pre-occupation with the political significance of the armaments race causes us to lose sight of the potential harm which may attend the peaceful applications of nuclear energy. During the stalemate which will result when all opposing nations have each perfected enough bombs mutually to destroy each other's cities in one single holocaust, reactors of ever increasing power and diversity will be built in growing numbers and at diverse places across the surface of this globe. The creation of these atomic powered units and their subsequent operation or periodic dismantlement may, but need not, bring health hazards even greater than those attributed to the bombs which sensible politicians will keep safely locked away as long as possible. Fortunately, the issue being in the domain of mathematics, physics, and chemistry there should be an engineerable remedy for each predictable danger.

Some of the non-radioactive substances which play a part in the nuclear energy programs are capable of producing tissue effects of unusual complexity and ominous portent. Fortunately, as compared with the fantastic biological scope of radioactive elements, there seems as yet to be a limit

\*Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

\*\*Formerly Director, Saranac Laboratory. Presently at: Institute of Industrial Health and Department of Pathology, University of Michigan, Ann Arbor.

to the range of stable elements which may prove dangerous to man. It may come as a surprise to many, however, to ascertain the full extent of the noxious environmental factors to which human beings may already be exposed, in the generation of nuclear power, during the stages preceding the achievement of radioactive energy. Figure 1 emphasizes the fact that, despite all that is already known about occupational diseases, there are so many mineral substances whose biological effects remain unknown that we have no means of predicting the nature of future hazards. The atomic age has rendered important a great many minerals and elements which previously had no health relevance for man. The present account is limited to respiratory system hazards, and therefore will deal with part of the problem only.

#### *Sources of Exposure*

##### *Mining and Transportation of Raw Materials:*

In gathering the raw materials needed for the production of nuclear energy, almost the full range of human occupations plays a part. Most of the attendant hazards are not new. Some activities are surprisingly mundane, e.g., collecting bones of deceased animals on the Transvaal High-

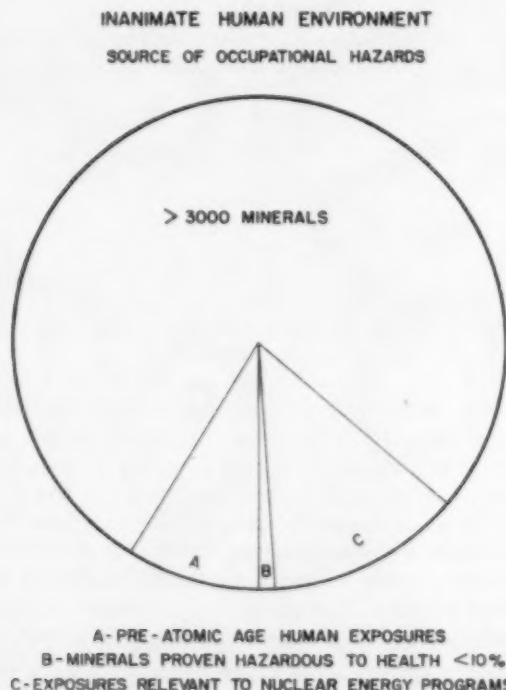


FIGURE 1: Diagram showing the ratio of known hazardous mineral substances to the whole mineral kingdom, and forecasting the range of new minerals to which human beings will be exposed as a result of the mining activities necessary to projected nuclear energy programs.

veld. Others are highly eclectic, e.g., isolation of heavy water. In essence, however, the main respiratory hazard during this stage derives from mining. As silica forms a major constituent of the earth's crust, and as the minerals which are of importance to atomic energy programs are embedded within a diversity of rock formations, silicosis once more asserts itself as a relevant health hazard. In mines, such as those in South Africa, where the recovery of uranium has been profitably added to the quest for gold, no new hazard has necessarily arisen. As the value of the uranium increases and that of the gold declines, fuller recognition will have to be accorded to the relationship of the residual pulmonary health problem to the atomic energy program. Hundreds of miners annually develop silicosis or its complications, chiefly tuberculosis, in the South African mines, despite energetic engineering and medical efforts to prevent these diseases. A great deal of progress has been made in reducing the ravages of dust-caused disability and death.<sup>1</sup> There is not yet in sight any hope of conquest of this problem, and at least some of the progress made may have been illusory for there has been a steady shift of the clinical emphasis from mere radiographically demonstrable pneumoconiosis to pulmonary disability as the dominant issue.<sup>2</sup>

The demand for uranium is so tremendous that new mining ventures have been initiated in almost every section of the globe. Most of the new mines have started off as small operations exploring promising ore bodies. Many amateurs have taken part in these pursuits and there is reason to believe that proper dust hygiene measures have not always been observed. Undoubtedly when the effects of excessive quantities of inhaled rock dust commence to show, we shall yet encounter some of the victims of these earlier undisciplined enthusiasms. It is just as well that more physicians appreciate what constitutes silicosis.

In at least one other region the search for uranium has stirred up an old problem. At Schneeberg and Joachimstal in the Carpathian mountains, now behind the Iron Curtain, the mines, which for centuries have yielded abundant uranium, cobalt, and arsenic, have over the years acquired such a bad reputation as health hazards that the popular designation for these ancient mines has long been "the death shafts."<sup>3</sup> Much of the evil reputation of these pits probably reflects earlier inadequate hygiene standards and it is to be hoped that the Russian technologists have since overcome this problem. However, the high pulmonary cancer rates in these mines has focused attention on the possible pathogenic role of minerals other than silica, for it is fairly well established<sup>4, 5</sup> that inhaled quartz dust is not carcinogenic. Speculation has ranged from the role of the radioactive uranium and the specific influence of cobaltic compounds to the neoplasogenic potency of arsenious acid released by subterranean fungi.

The foregoing issue illustrates the general problem. Besides the known hazard constituted by inhaled crystalline free silica we are today faced with the problem of defining the precise biological action of a great many minerals associated with radioactive ore bodies. A conservative estimate of the number of minerals to which human beings may theoretically be

exposed through the expansion of modern industry, exceeds 3,000 separate varieties.<sup>6</sup> The demand for uranium, strontium, and lithium has already brought miners into contact with a considerable number of minerals additional to those previously encountered as an environmental health hazard in the process of catering to civilization's basic raw material needs. The problem is even broader than this.

For making a hydrogen bomb or to build a reactor, far more elements are exploited than merely the well publicized ingredients, uranium, strontium, lithium, or deuterium. Thermonuclear bombs, radiant energy reactors and intercontinental ballistic missiles are man's highest technological achievements. To create these, not only the immediate active elements are needed, but also a host of ancillary substances which either are a material factor in compounding the final product or serve a useful purpose at an intermediate stage. Substances such as beryllium, boron, graphite, zirconium, lead, and mercury all play a substantial role. In gathering together all these elements, diversified mining activities are involved. Bombs and reactors also have created problems in structural engineering. Vast caverns have been hollowed out in volcanic rock, both as storage depots and for the reception of radioactive wastes. Rocks have been crushed and pulverized to make concrete. Asbestos and glass wool have been invoked as insulating materials. In the meanwhile, the range of useful products is continually being expanded by the discoveries of the research chemists and physicists. The rare earths, once so truly rare, are currently being advertised as available by the carload. Garnering these diverse products devolves on the activities of miners. These men therefore form the first phalanx of those who may theoretically be exposed to non-radioactive respiratory tract hazards in the diversified atomic energy programs.

#### *Metallurgical and Chemical Processes:*

The next phase of the problem is encountered in the plants where the desired elements are recovered from ore bodies, refined, and subsequently compounded or alloyed as required for specific purposes. The potential health hazards in this phase are great and literally volumes have been written about experiments to track down the toxicity of single elements and their compounds.<sup>7, 8</sup>

Uranium has for some time served as the classical example. For the present purpose we are not concerned with its radioactive properties. The principal uranium ores are pitchblende, carnotite, autunite, and tobernite. The former two are the more important. In pitchblende the uranium oxide content may range from 10 to 70 per cent. Other elements which may be present are radium, lead, aluminum, arsenic, calcium, iron, magnesium, manganese, nickel, cobalt, molybdenum, sulphur, fluorine, silicon, titanium, sodium, carbon, helium, hydrogen, oxygen, cadmium, phosphorous, chlorine, osmium, palladium, platinum, copper, and various of the rare earths. The uranium usually occurs in the form of  $\text{UO}_2$  and  $\text{UO}_3$  in ratios which correspond closely to  $\text{U}_3\text{O}_8$ . Carnotite has been given the formula:  $\text{K}_2\text{O} \cdot 2\text{UO}_3 \cdot \text{V}_2\text{O}_5 \cdot 3\text{H}_2\text{O}$ . While the potassium and vanadium form the dominant constituents, lead, radium, barium, and calcium



are prominent constituents and traces of numerous other elements also are present. In autunite, calcium and phosphorous, and in torbernite, copper and phosphorous are important constituents. From the foregoing it should be clear, therefore, that in coping with inhalation problems linked with uranium ore dust, the uranium may be the dominant agent or may be the lesser constituent.

The extraction of uranium from its ores is done largely by means of nitric and hydrochloric acids. The uranium is released from the uranyl nitrate by ether. Being multivalent, the liberated uranium forms compounds with valence dominances of 3, 4, 5, or 6. The hexavalent uranium is most stable in aqueous solutions. Of the various compounds to which human exposures may occur, the oxides ( $\text{UO}_2$ ,  $\text{UO}_3$ ,  $\text{UO}_4$ ,  $\text{UO}_4 \cdot 3\text{H}_2\text{O}$ ,  $\text{U}_3\text{O}_8$ ), fluorides ( $\text{UF}_4$ ,  $\text{UF}_6$ ,  $\text{UO}_2\text{F}_2$ ), diuranates ( $\text{Na}_2\text{U}_2\text{O}_7 \cdot 1\frac{1}{2}\text{H}_2\text{O}$ ,  $(\text{NH}_4)_2\text{U}_2\text{O}_7 \cdot 4\text{H}_2\text{O}$ ), chloride ( $\text{UCl}_4$ ), nitrate ( $\text{UO}_2(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ ) are best known. There naturally are numerous other compounds, such as the hydride ( $\text{UH}_3$ ), carbides ( $\text{UC}$ ,  $\text{U}_2\text{C}_3$ ,  $\text{UC}_2$ ), nitrides ( $\text{UN}$ ,  $\text{UN}_{1.5-2}$ ), acetate ( $\text{UO}_2(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}$ ) etc., which may be of importance at some other stage.

The diversity of problems encountered may be illustrated by means of yet another element which is of crucial importance in practically all phases of atomic energy production. Because of its peculiar lattice structure, beryllium is uniquely valuable as a source of neutrons, particularly as it remains stable at the high temperature generated under nuclear bombardment. This use has greatly augmented the exploitation of the element. Prior to 1931 less than 100 pounds of the metal were consumed annually for all industrial purposes in the United States. Ten years later the annual consumption approached 30,000 pounds. By 1950 this use had increased a further five-fold (approximately 150,000 pounds). Recent estimates predict that by 1960 more than a million pounds of beryllium will be needed to support the nuclear reactor programs in addition to the multifarious metallurgical uses of the element (Fig. 2).

Beryllium is extracted chiefly from beryl (beryllium aluminum silicate). The beryllium content of the ore varies between 10 and 13 per cent. About 15 to 20 per cent of the ore is aluminum and 65 to 70 per cent is silicon dioxide. To reduce the ore to beryllium oxide either a sulphate or a fluoride process may be used. Several other variations are also invoked for special purposes. During these phases plant personnel may thus become exposed not only to the milled ore dust but also to compounds such as beryllium oxide, beryllium sulphate, beryllium fluoride, beryllium oxyfluoride, basic beryllium carbonate, beryllium phosphate, beryllium chloride, beryllium nitrate, and beryllium stearate. The final product, of course, is the beryllium metal. This is the form in which the element is used for atomic energy purposes. Before it can be made available, many inhalation exposures would be possible if inadequate hygiene precautions are exercised.

The list of "new" elements which yield health problems between the phase of mining and the application of the substance in bombs or reactors is



growing steadily. In practically all instances the elements are refined to their pure state and new compounds are manufactured. Thus series of wholly artificial hazards may be created.

#### *Bomb Manufacture and Reactor Installation*

For security reasons many of the phases involving the use of specialized materials in the manufacture of thermonuclear weapons remain undisclosed. The role of radioactive materials also predominates during this phase. However, it is no secret that the plutonium, the lithium and the beryllium have to be housed in appropriate containers, and it takes but little imagination to recognize that in some measure certain metallic constituents of these bombs have to be machined or welded with the sequential release of respirable particles or fumes.

The principles of construction of reactors are a little better known. Even high school students are aware of the role of the graphite cores of the atomic piles, the significance of special metallic coolants (e.g., sodium), the value of lead shielding, etc. Any constructional process

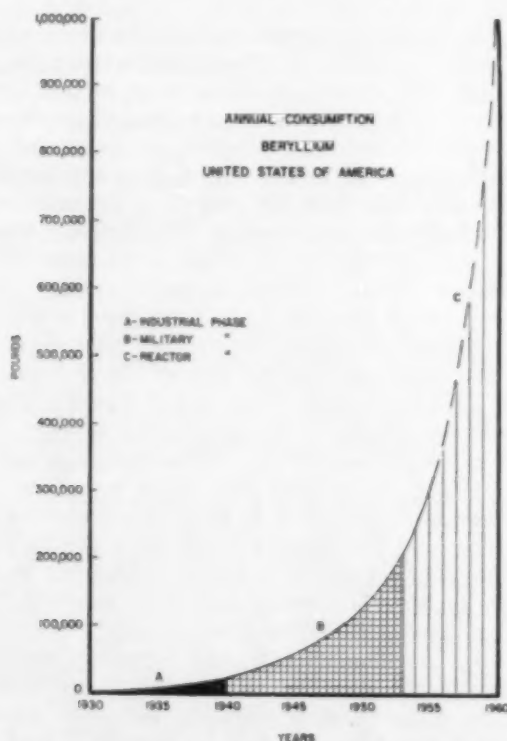


FIGURE 2: The graph illustrates the dramatic increase in the annual consumption of beryllium in the United States. Prior to 1930 less than 100 pounds were used annually. The 10,000 pound level was reached just before the Second World War. From 1939 to 1947 the consumption of beryllium increased from less than 20,000 pounds to more than 100,000 pounds.

which involves the uncontrolled machining or welding of some of these stable element components of the reactor may theoretically lead to the release of a respiratory system hazard. All of these engineering ventures are so new and such excellent precautions have generally been taken to avoid risks, that very little specific information is currently available about health problems. The theoretical possibility remains, however, that at some time in the future some essential precaution may be overlooked. It is just as well, therefore, that the construction, maintenance, and dismantling of reactors be carefully scrutinized for possible sources of health hazards, not only because of the radioactive elements, but also because of the unusual non radioactive substances which are involved.

### *Basic Biological Effects*

To review, in a paper of the present scope, the full range of biological effects provoked by such a diversity of stable elements which may yield respirable hazards, is obviously impracticable. Each inhaled substance can cause lesions of a characteristic type and distribution. However, there are certain broad principles which unify the pathology resulting from exposures to these individual substances. These basic patterns will now be briefly reviewed and illustrated with specific examples.

#### *Pulmonary Lesions:*

Being the portal of entry of inhaled particles, fumes, or gases, the respiratory tract naturally requires first consideration. These foreign agents may be arrested at any point in their course to the alveolar membrane, if they are of an insoluble or slowly soluble type. In such instances they often remain embedded in the tissues and then are identifiable by petrographic methods (Figs. 3A and 3B). This is often a great help in differentiating the resultant lesions from disease processes of biological origin. If the etiological agents are readily soluble, they may traverse the pulmonary tissues to become lodged in some other part of the body. In such cases no local clue may be discovered, but appropriate study of distant organs, such as the bones, may continue to furnish the necessary diagnostic information.

Because of the multiplicity of levels at which the inhaled particles or gases may impinge, the resulting lesions may range from tracheitis, bronchitis, and bronchiolitis to the strictly parenchymal pulmonary reactions. At each of these sites the responses may range from acute and subacute to the chronic in respect of their rate of development. Their grades of severity may be either slight, moderate, advanced, or even fatal. In the area of distribution the responses may be localized, multifocal, diffuse, or universal. With respect to permanence, the lesions may vary markedly. Some are transient, either wholly or partially, while others are irreversible, with or without progression. Qualitatively each lesion may be either exudative, hyperemic or ischemic, catarrhal, necrotizing, degenerative, inflammatory, or proliferative. Cell changes involving abnormal mitosis and ultimately neoplasia may occur. Sometimes several of these types of reaction may be found in the same lung, simultaneously

or successively. Phenomena such as sensitization and allergy apply in certain instances. Tolerance may develop in many cases. When inhaled simultaneously or successively, some substances act synergistically and produce a result of which neither component is separately capable. In other instances two agents may behave antagonistically and nullify the action of either one or of both. In a great many instances, too, the inhaled substances appear to have no local effect on the tissues of the respiratory system or evoke a negligible phagocytic defensive reaction only. Theoretically, too, some of these agents should prove beneficial. Regrettably, there are but few instances of the latter phenomenon.

Dosage plays a great part in determining the pattern of lesions induced by individual noxious agents. The correlation may, however, be either positive or negative. While some agents have a relatively high threshold, the liminal dose is infinitesimally small in other instances. Rate of exposure similarly serves as a determinant of pathology. Intermittent exposures reduce the reaction in some cases and enhance the response in other instances. In most instances, however, lesions regress on cessation of exposure, *pari passu*, with the elimination of the foreign agent from the tissues. In other instances the pathological processes progress in spite of the removal of the subject from the harmful environment. Not infrequently the tissue response is so retarded as only to manifest itself many years after the irritant substance had been introduced. In yet further instances the very withdrawal of the inhalation hazard is

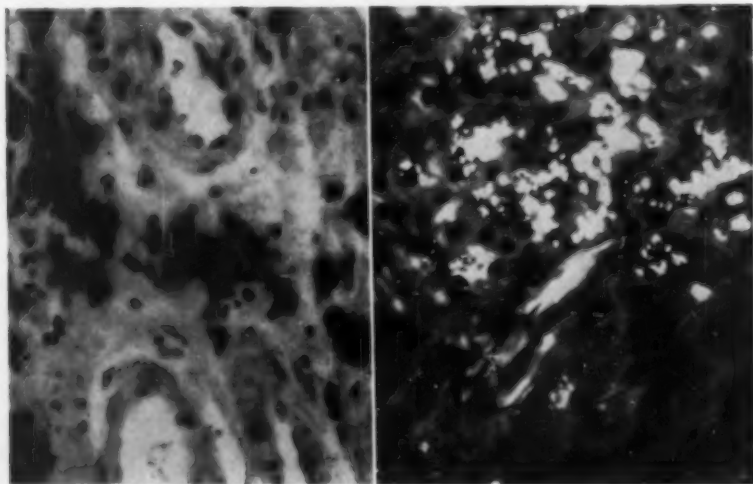


FIGURE 3A

FIGURE 3B

Figure 3A: Opaque mineral particles embedded in the lung tissue of a uranium machinist who developed chronic pulmonary granulomatosis, confirmed by biopsy (Hematoxylin and Eosin  $\times 800$ ).—Figure 3B: Brightly birefringent particles in the lung tissue of a beryllium worker with chronic pulmonary granulomatosis (Polarized Light  $\times 800$ ).

promptly followed by a more violent reaction than that observed during the phase of continuous exposure.

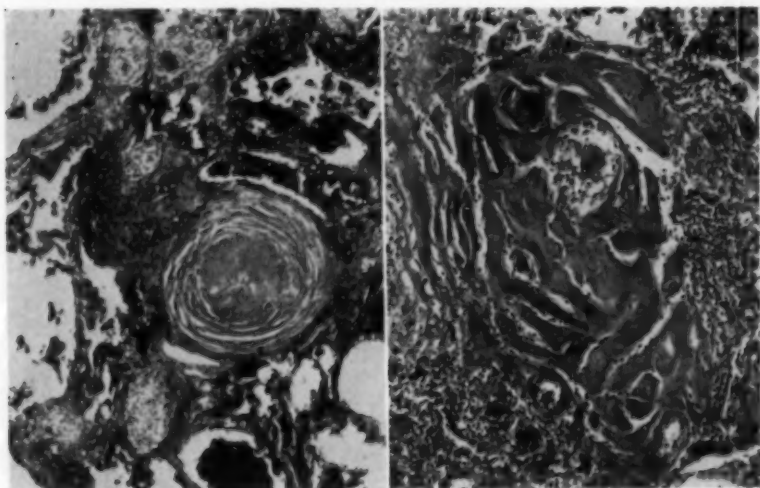


FIGURE 4A

FIGURE 4B

*Figure 4A:* Silicotic type of whorled fibrous nodule in the lung of a beryllium worker with no occupational history of quartz dust exposure (Hematoxylin and Eosin  $\times 65$ ).

*Figure 4B:* Irregular deposit of collagen in a granulomatous zone of the lung of a beryllium worker (Mallory  $\times 175$ ).

Secondary infection frequently plays a significant role in determining the course and outcome in specific syndromes. Tuberculosis is significantly related to the dust exposures in some instances but has no causal relationship in others. The tuberculous process may be enhanced by the pneumoconiosis or may in turn aggravate the latter. Nonspecific infections likewise are either facilitated or suppressed by the concurrent or prior inhalation of noxious dust particles, fumes or gases. The introduction of the foreign agent may either facilitate the entry of pathogenic bacteria and viruses or may augment the effects of organisms normally resident in the pulmonary tissues.

The foregoing formidable array of possibilities, coupled with the fact that for each element there may be multiple compounds and many physical states in which the noxious agent can enter the body, plus the ever-present possibility that exposures to many separate substances may occur simultaneously or successively, all help to complicate matters. It is fortunate, therefore, that so many inhaled agents are relatively inert.

The silicotic nodule is still today the hallmark of industrial pulmonary disease. Except in cases where there has been frank exposure to crystalline-free silica, whorled fibrous nodules are unusual occurrences among the group of diseases resulting from exposures to the elements which are of importance to nuclear energy production. Nodules such as these do, however, occur quite inexplicably in circumstances where no silica

exposures have been recorded or in the absence of adequate tissue levels of silica (Fig. 4A). More usually focal fibrous deposits assume bizarre shapes and are relatively readily identified as non-silicotic (Fig. 4B).

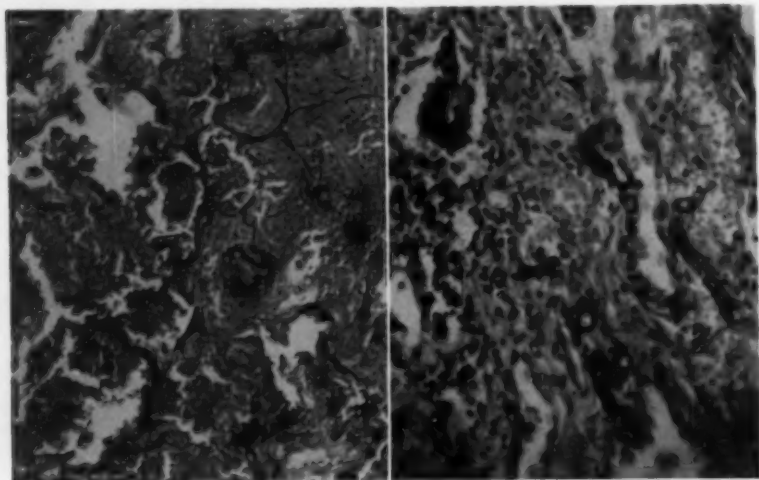


FIGURE 5A

FIGURE 5B

*Figure 5A:* Disruption of the elastic tissue as a delayed manifestation of the inhalation exposure to beryllium (Weigert's  $\times 160$ ).—*Figure 5B:* Mineral impregnated casts of pulmonary capillaries in an area of irregular granulomatous reaction in a beryllium worker (Hematoxylin and Eosin  $\times 350$ ).

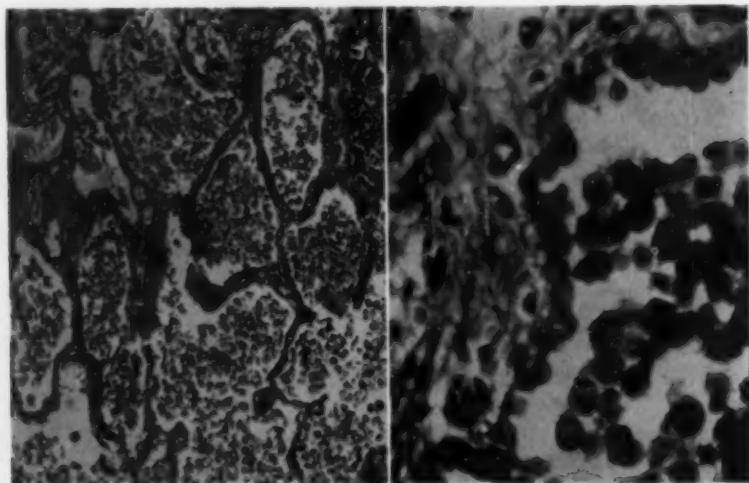


FIGURE 6A

FIGURE 6B

*Figure 6A:* Chronic macrophage catarrh into the alveolar spaces of the lungs of a beryllium worker (Mallory  $\times 190$ ).—*Figure 6B:* Epithelialization of a fibrosed alveolar wall with proliferation of cells into the alveolar spaces of the lungs of a beryllium worker (biopsy) (Mallory  $\times 1000$ ).



The frankly chemical nature of many of the foreign agents of this group often leads to tissue destruction. Such necrobiosis is the basis of several of the varieties of acute chemical pneumonitis. In cases which apparently recover, the results of the acute phase of reaction may persist in the form of destroyed elastic tissue and damaged capillaries (Figs. 5A and 5B). The damage to the pulmonary elastica may be the basis for later emphysema and the relationship may not be identified until a tissue biopsy or autopsy has been performed. Damage to capillaries may be a factor in the subsequent development of cor pulmonale.

While pulmonary cellular catarrh is usually a feature of the early subacute phase, it may persist as a chronic reaction (Fig. 6A). In essence the catarrh represents a constant outpouring of macrophages. There is, however, a further variety of catarrhal response, fortunately rare, in which the discharged cells are of epithelial origin (Fig. 6B). This variety is of more serious import owing to its close approximation to neoplasia.

The best popularized, though not necessarily the most characteristic lesion associated with the inhalation of atomic energy-related stable element particles is the granuloma.<sup>9</sup> This unit lesion assumes many forms but essentially is based on an alveolar membrane and consists of a core of macrophages and giant cells and a surrounding zone of plasma cells supported by reticulum (Fig. 7A). Not infrequently such granulomata are perivascular in location (Fig. 7B). This simply denotes that foreign agent-laden macrophages managed to travel some distance in the pulmonary lymphatic channels before becoming arrested. This result ensues if the foreign agent is less immediately toxic. The ultimate effect, however,

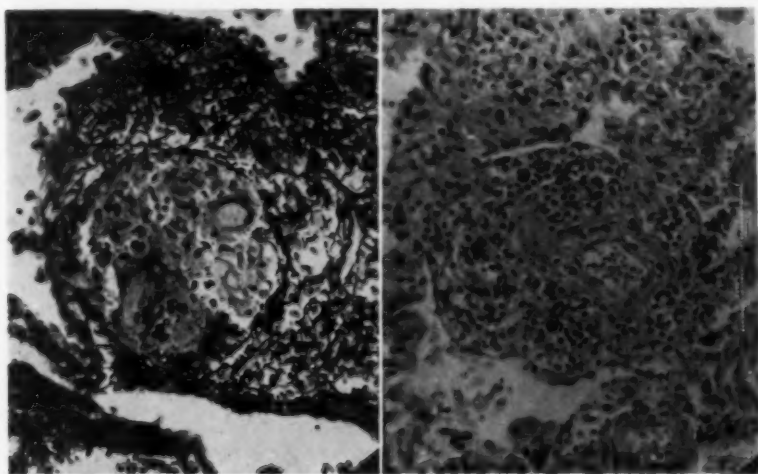


FIGURE 7A

FIGURE 7B

*Figure 7A: Alveolar wall granuloma in the lung of a uranium machinist (biopsy) (Foote's Reticulin Stain,  $\times 350$ ).—Figure 7B: Perivascular fibrocellular granuloma in the lung of a beryllium worker (Hematoxylin and Eosin,  $\times 300$ ).*

may be more disastrous, for occlusion of the affected blood vessel is likely to induce greater disability than would follow the focal loss of alveolar membrane function.

The granulomata have been further characterized through the possession of inclusion bodies of several varieties. The origin of the crystals (Fig. 8A) which are often found in these cases is not clear. Conchoidal bodies (Fig. 8B) have been regarded as separate entities. They probably are excretion products of giant cells. It has been noted that these interesting structures are prevalent in persons exposed to certain groups of elements and less common in other workers exposed to different types of noxious agents. This may have diagnostic significance but we require more data in order to be sure.

*Sequelae:*

Among the more obvious local sequelae of the respiratory tract reaction to the inhalation of various stable elements used in the generation of nuclear energy is involvement of the pulmonary adnexae. Earlier experiences with asbestosis and silicosis have focused attention on the exaggerated pleural damage in the former and the far-ranging lymphoid tissue involvement in the latter disease. It is interesting, therefore, to find that the substances which have recently become so important, may behave in this fashion too, though they do not necessarily reproduce identical patterns. In isolated instances, however, the pulmonary adnexae become diseased without the development of a prior or concomitant re-

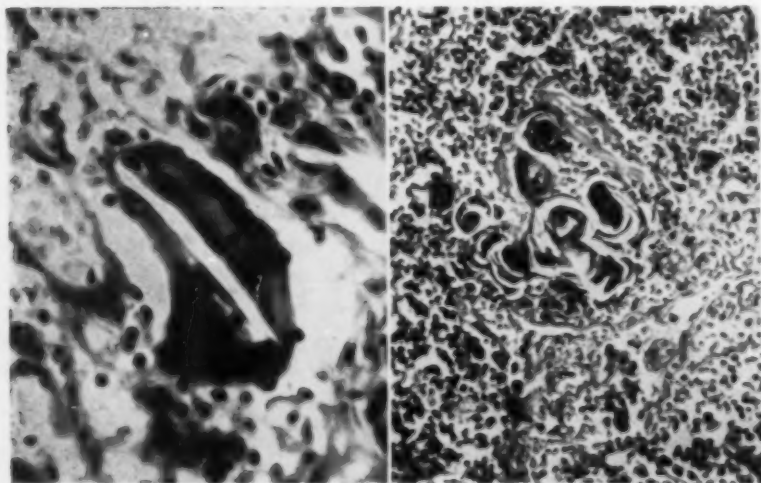


FIGURE 8A

FIGURE 8B

*Figure 8A:* Crystal cleft within a multinucleated giant cell in a beryllium worker with pulmonary granulomatosis (Hematoxylin and Eosin,  $\times 800$ ).—*Figure 8B:* Conchoidal body in a granulomatous area of the lung of a beryllium worker (Hematoxylin and Eosin,  $\times 300$ ).



action in the lungs or air passages. In some cases there can be advanced pulmonary disease without spread to the regional lymph nodes or pleura.

Cor pulmonale constitutes another serious but immediate sequel to the pulmonary disease caused by the group of inhaled substances relevant to atomic energy programs. In the majority of cases the pulmonary hypertension arises directly as a result of the progressive occlusion of capillaries and small blood vessels. This effect is produced by any of the classical mechanisms underlying the development of primary cor pulmonale,<sup>11</sup> but emphasis appears to be placed on the destruction of the pulmonary capillary bed by vascular necrosis (Fig. 9A) and pericapillary fibrosis (Fig. 9B). The relationship between the pericapillary reaction and inhaled particulate matter often is immediately apparent. Occlusion of small blood vessels through endarteritis obliterans is a not uncommon occurrence (Figs. 10A and 10B). Blood vessels may also be narrowed by perivascular cell infiltrations and adventitial cicatricial stenosis. Right ventricular enlargement and strain also undoubtedly result physiologically through chronic hypoxia originating in granulomatous lesions of the alveolar walls and in the emphysema which so commonly is associated with metallic inhalation hazards.

Practically all the lesions observed in human subjects have been reproduced experimentally. The characteristic granulomata of beryllium disease and the proliferation of alveolar wall epithelium have been particularly well reproduced. A much more ominous sequel, not yet proved in man but quite readily producible in rats by means of various beryllium compounds, is neoplasia.<sup>10</sup>

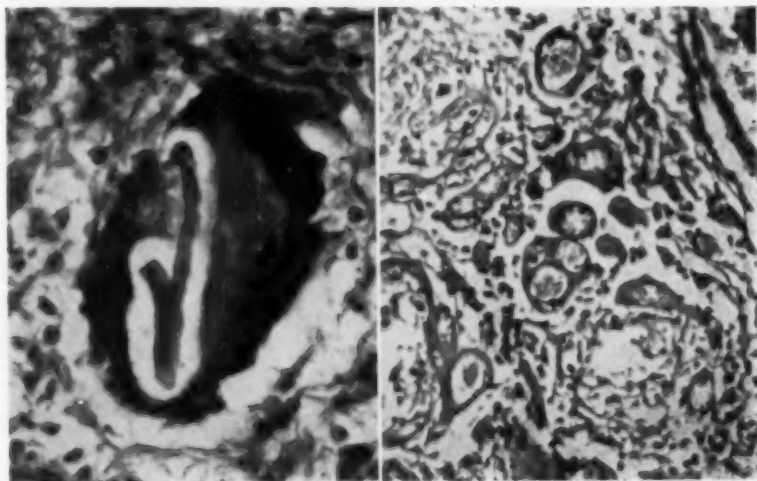


FIGURE 9A

FIGURE 9B

*Figure 9A:* Remnant of a necrosed small blood vessel phagocytosed by a multinucleated giant cell in the lung of a beryllium worker who died of cor pulmonale (Hematoxylin and Eosin,  $\times 800$ ).—*Figure 9B:* Pericapillary fibrosis in the lungs of a beryllium worker who died of cor pulmonale (Mallory,  $\times 350$ ).

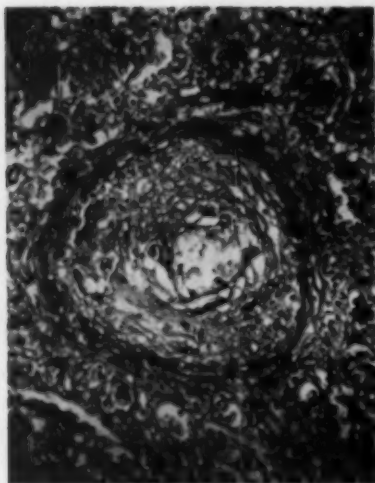


FIGURE 10A

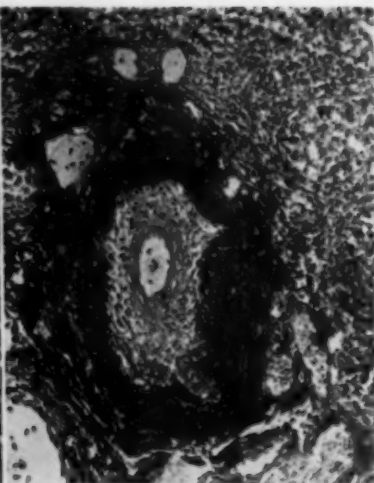


FIGURE 10B

*Figure 10A:* Endarteritis obliterans of a small blood vessel in a granulomatous area of the lung of a beryllium worker who died of cor pulmonale (Mallory,  $\times 320$ ).—*Figure 10B:* Perivascular cell infiltration and endarteritis obliterans of a medium-sized artery in the lung of a beryllium worker who died of cor pulmonale (Weigert,  $\times 175$ ).

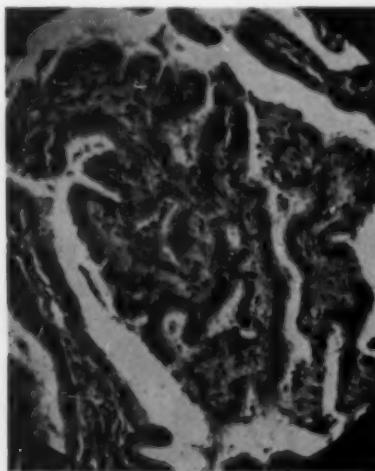


FIGURE 11A

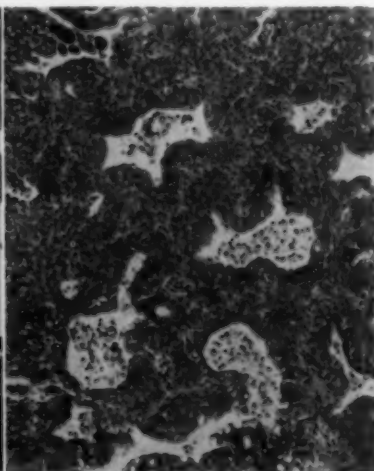


FIGURE 11B

*Figure 11A:* Pulmonary papillary adenocarcinoma which metastasized to other organs of a rat exposed by inhalation to an aerosol of beryllium sulphate for 6 months and then allowed to reside in normal air for 10 months until killed (Hematoxylin and Eosin,  $\times 300$ ).—*Figure 11B:* Squamous carcinoma in the lung of a rat exposed by inhalation to an aerosol of beryllium sulphate for 6 months and then allowed to reside in normal air for 10 months until killed (Hematoxylin and Eosin,  $\times 175$ ).

Characteristic features of these pulmonary tumors are their great prevalence, their multifocal origin, their pleomorphism (Figs. 11A and 11B), malignancy, and their origin in peribronchiolar alveolar membranes rather than the bronchial mucosa. Astonishing discoveries concern the exceedingly minute doses which can effectively induce neoplasia and the great interval which may elapse between the period of exposure and the inception of the new growth. Frequently no traces of the original chemical irritant are demonstrable in the lung tissue by the time the cancer has formed.

*Complications:*

As a result of inhalation exposures to various of the stable elements used in atomic energy programs, lesions may be provoked in more remote structures of the body. The capacity of the lung to absorb soluble compounds is stupendous. On being inhaled such substances pass to remote organs with almost the same facility as happens when they are injected intravenously. A fairly large proportion of the compounds of the various elements important to nuclear energy programs are quite soluble. They may, therefore, be rapidly transported from the lungs to organs such as



FIGURE 12: Osteogenic sarcoma which developed in the femur of a rabbit 13 months after it had received 1 gram of zinc manganese beryllium silicate in 20 bi-weekly intravenous injections. Injections of zinc, manganese, and silica separately or combined did not induce sarcomatosis. The total dose of beryllium administered was 29.8 mg.

the liver, kidney, suprarenal, spleen, and bone. Some of the compounds affect these distant organs without even provoking demonstrable pulmonary changes while others also affect the lungs in transit.

Degenerative changes in the liver, kidney and suprarenal result in the obvious metabolic disturbances. Long before dysfunction becomes clinically manifest, however, there may be subtle enzyme and endocrine changes, recognition of which may serve as sensitive indicators of incipient systemic metallic toxemia. Deposition of these chemical agents in bone and bone marrow may have serious consequences. Anemia may be the first result. Polycythemia, on the contrary, may also arise both through local action on the myelopoietic system or as a sequel to the chronic hypoxia due to extensive lung damage. Leukemia is to be anticipated but no proved case has been attributed to stable chemical elements. Bone sarcoma has, however, definitely been produced under experimental conditions.<sup>12</sup> Osteogenic sarcomata were first produced by injections of a fluorescent tube powder containing zinc, manganese, silica, and beryllium (Fig. 12). Subsequently this form of neoplasm was successfully provoked by injections of beryllium oxide only. This occurrence, the more particularly because it is a delayed phenomenon, imparts an ominous significance to the passage of elements across the pulmonary barrier. The danger of bone sarcoma from radioactive fall-out is already much under public scrutiny. The possibility of such a complication through exposures to some of the non-radioactive elements used in nuclear energy programs should not be overlooked.

#### *Discussion*

Precise knowledge of the nature of the biological response to the various elements to which men may become exposed in the process of developing atomic energy cannot be achieved without acquiring a concept of the tolerances permissible to the human system. Our understanding of the nature of the disease which may result from such exposures, limited as it is, has far outstripped our information on threshold values. This stricture applies with equal force to almost every phase of the problem. Vast sums have already been spent on research, particularly as it pertains to uranium and beryllium. While many fundamental truths have been uncovered, our knowledge is far from precise. The comprehensive investigations on the toxicity of uranium, sponsored by the Atomic Energy Commission, were limited by the crash program nature of the study enforced by the military emergency. Much was discovered about the effects of acute and subacute exposures to uranium ores and uranium compounds. The influence of long-term exposures and the deferred effects of transient inhalation of uranium compounds still have to be worked out. Many answers will be furnished by the close supervision of uranium miners and plant personnel which already has been instituted in many quarters. Without further experimental research, however, the possibility remains that human beings will serve as the experimental subjects whereas rats and guinea pigs could furnish the answers to extant problems.

The uranium phase of the atomic energy program is probably likely to

constitute the lesser hazard for the reason that processing and use of the element is under such direct supervision of competent scientists. It is more probable that other elements may receive insufficient attention. Beryllium may serve as a typical example. Enthusiasms for research on the biological action of this crucial element seem to be waning. Facile assumptions are current that we have all the answers, that the metal and its compounds are under adequate engineering control, and that many of the claims about the toxicity of the substance are spurious and exaggerated. There seem to be more experts on this subject who have never seen a case of beryllium poisoning or who have never conducted an experiment, than there are true connoisseurs. Those of us who have inquired into the problem first-hand are impressed with the paucity of our facts, the magnitude of the enigma and the urgency of the need for precise information. The fact that a million pounds of beryllium metal may soon be available for the construction of nuclear reactors focuses attention on the need for exact information on health hazards. Exposures are unlikely in newer manufacturing plants where serious efforts at health protection have been instituted. Danger of exposure is more probable at the points of exploitation of the metal. We have proved, for instance, that beryllium fluoride, in a dose as low as 1.36 gamma per cubic foot of air (equal to 0.26 gamma beryllium) is a very effective pulmonary carcinogen in rats. While the temptation may exist to assume that the effective dose for man will have to be proportionate to his greater body weight, it should be recognized that each pulmonary cancer may have its origin in but a single vulnerable cell. We have no precise way of knowing whether a human lung cell will need more or less beryllium exposure, to evoke a latent neoplastic tendency, than will a rat lung cell. Perhaps an exposure to beryllium at a level of 0.26 gamma per cubic foot will be just as dangerous for man as it is for the rat. Only further research will help furnish the answer. In the meanwhile, it may be pointed out that a dose of 0.23 gamma beryllium per cubic foot is really infinitesimally small. A single pound of the million pounds of beryllium metal soon to be in use, can produce a concentration of 0.26 gamma per cubic foot in a zone 100 feet deep over an area of approximately 1 square mile!

Diagnosis of an industrial disease is usually facilitated by an exact occupational history. For reasons of security it is possible that potential victims of inhalation exposures to nonradioactive elements may fail to disclose to their physicians significant phases of their work record. This matter would not be mentioned here if it had not already occurred. The common enemies with which we are confronted are disease, disability, death, and genetic decay. Secrecy about symptoms and exposure will help these foes. Every physician should become fully conversant with the precise health implications of current nuclear energy programs. The widely publicized pronouncements of well-meaning veteran physicians, who may be very ill-informed about technical details, do little good and may cause needless panic. More effective control over health hazards will result from the proper instruction of all physicians. Atomic energy problems which



once were limited to Oak Ridge or Los Alamos will soon be an issue in scores of cities, large and small. Thus far ignorance about the problem has been understandable. Ignorance in the future will be inexcusable.

The introduction of new elements to which human beings may be occupationally exposed has set a premium on new diagnostic standards. The aim should be to recognize each case so early that construction, maintenance, military, and hygiene engineers can be immediately alerted to the fact that their efforts to eliminate a hazard which has been overlooked should be redoubled. This is the ideal. We may as yet be far from attaining such perfection. Recognition of the clinical forms of these occupational diseases is important, but it essentially comes too late in those instances where a long period intervenes between the phase of effective exposure and the first clinical manifestation of ill health. New laboratory methods, perhaps chiefly those in the domain of enzyme chemistry, may furnish the earliest clues.

Several medico-legal questions are pertinent. Current statutes of limitation debar from just compensation many victims of the deferred sequelae of these occupational diseases. Responsibility for the so-called "neighborhood cases" has not yet been adequately settled. In view of the national importance of the whole program of nuclear energy production, it is patently unjust to continue to permit individual companies to shoulder the full burden of culpability, when all citizens are the beneficiaries of the collective venture. Alarmism and ignorance has probably promoted fraudulent and frivolous compensation claims and consequently seem to have stiffened the defense of some corporations to the point of unreasonableness. Cases which should have been settled out of court have been exposed to the full gamut of legalistic dialectics. Juries, whose minds are repeatedly inflamed by a barrage of sensationalistic publications or who may be swayed by political adherences, hardly constitute the proper tribunals to adjudicate on problems about which the scientists are still so grievously ignorant!

No progress will be made without unremitting research on these multitudinous questions. The scope of disease should be explored in experimental animals of appropriate species and over sufficiently long periods in order to anticipate the occurrence of any of these problems and by effective action to eliminate the hazard before it becomes material. Hygiene standards obviously should be revised, now that we are aware of the fact that several of the newer elements to which man may be exposed behave like trace elements and are effective in extremely minute quantities. Almost nothing is known about antidotes and therapeutic agents. It is sheer pessimism to assume that once a workman has been exposed to a significant dose of carcinogenic beryllium nothing more can be done for him. We already know, for instance, that aurin-tri-carboxylic acid readily combines with various beryllium compounds. This may not be the antidote, but without further research on substances such as this, no prophylactic or therapeutic agent is likely to be discovered.

## SUMMARY

1. The military and peacetime nuclear energy programs have greatly expanded the potential scope of human exposures to new and old dust, fume, and gaseous environmental hazards. A large proportion of these new dangers may originate in the biological action of stable elements rather than radioactivity.

2. Exposures are possible in the operations of assembling raw materials, during the processes of extracting, refining, and chemically modifying the various key elements, and in the manufacture of thermonuclear weapons and peacetime reactors.

3. Among the various stable elements, to which exposures are likely, beryllium has the worst record as an inhalation hazard, and this is unfortunate as its strategic nature has greatly increased its use. While some of the newly introduced elements are highly dangerous, a gratifying number appear to be entirely inert. Many of the lesions which may occur in exposed personnel undergo spontaneous remission.

4. Practically all hazards should be preventable by appropriate engineering methods.

5. Various characteristic pulmonary lesions are discussed. Among these the local accumulation of foreign particles, focal fibrosis, cellular and stromal necrosis, chronic macrophage catarrh, epithelialization of alveolar walls, granuloma formation, and vascular damage are the most spectacular.

6. Many of the lesions observed in man have been experimentally reproduced. It has also been possible to induce pulmonary cancer in rats through exposures to various compounds of beryllium even at very low dosage levels.

7. Problems still to be solved, besides methodical, experimental and clinical exploration of the full range of substances to which human beings may be exposed, are: threshold levels of toxicity, especially in connection with prolonged exposures; differential responses in animal species and their applicability to man; precise diagnostic criteria, particularly in life; medico-legal difficulties created by the delayed occurrence of disease after exposure and the national importance of the nuclear energy program; antidotal and therapeutic agents. Only further research can furnish the necessary answers.

## RESUMEN

1. Las obras de energía nuclear de tipo militar o pacífico han acrecentado el alcance de las exposiciones humanas a polvos nuevos o viejos, humos, y a riesgos ambientales gaseosos.

Una gran proporción de estos nuevos peligros pueden originarse en la acción biológica de elementos estables más bien que a la radioactividad.

2. Durante el ensamblado de materias primas es posible que haya exposición, así como durante los procesos de extracción, refinación y modificación química de varios elementos esenciales y en la manufactura de armas termonucleares o en la de reactores para fines pacíficos.



3. En los diversos elementos estables a los que es posible exponerse, el berilio tiene el peor record como riesgo de inhalación y esto es muy infortunado porque su naturaleza estratégica ha aumentado mucho su uso. Si bien algunos de los elementos nuevos son altamente peligrosos, un número satisfactorio de ellos parece ser completamente inerte. Muchas de las lesiones que pueden sufrir el personal expuesto, puede tener regresión espontánea.

4. Prácticamente todos los riesgos deben ser prevenibles por métodos de ingeniería adecuados.

5. Se discuten los aspectos de varias lesiones pulmonares. Entre ellas la acumulación local de partículas extrañas, fibrosis local, necrosis celular y del stroma, el catarro macrofágico crónico, la epitelización de las paredes alveolares, la formación de granuloma y el daño vascular, son de las más impresionantes.

6. Pueden reproducirse experimentalmente muchas de las lesiones observadas en el hombre. También se ha podido producir cáncer primitivo en las ratas por medio de exposición a varios compuestos de berilio aún a muy baja dosificación.

7. Hay problemas aún por resolver aparte de los que dependen del método, de la exploración experimental y clínica de todas las substancias a las que se pueden exponer los humanos; tales son: Umbrales de toxicidad, especialmente en relación con largas exposiciones; respuestas diferentes en las especies animales y su aplicabilidad al hombre; criterio diagnóstico preciso, especialmente durante la vida; dificultades médico-legales creadas por el acaecimiento de enfermedad tardíamente después de la exposición y la importancia nacional de los proyectos de energía nuclear; los agentes terapéuticos y los antidotos. Sólo la investigación ulterior puede dar las respuestas necesarias.

#### ZUSAMMENFASSUNG

1. Die militärische und zivilen Kernenergieprogramme haben die potentielle Reichweite der Exposition des Menschen gegenüber den Umweltzufällen an neuem und alten Staub, Rauch und Gas beträchtlich ausgedehnt. Ein grosser Anteil dieser neuen Gefahren hat möglicherweise seinen Ursprung eher in der biologischen Aktion von stabilen Elementen als in der Radioaktivität.

2. Exposition ist möglich bei den Manipulationen der Sammlung des Rohmaterials, im Verlauf der Prozesse der Extraktion, der Reinigung und chemischen Modifizierung der verschiedenen Schlüsselemente, sowie während der Handhabung der thermonuklearen Waffen und der Zivilen Reaktoren.

3. Aus der Reihe der verschiedenen stabilen Elemente, denen gegenüber eine Exposition wahrscheinlich ist, hat des Beryllium das schlechteste Zeugnis als ein zufällig zu inhalierender Stoff, und nun liegt dies unglücklicherweise gerade so, dass jetzt dank seiner strategischen Natur seine Verwendung stark zugenommen hat. Während einige von den neu-eingeführten Elementen sehr gefährlich sind, scheint eine erfreuliche

Anzahl gänzlich unwirksam zu sein. Viele der Laesionen, die bei gefährdetem Personal eintreten können, unterliegen einer spontanen Remission.

4. Praktisch alle Zwischenfälle müssen sich verhüten lassen durch geeignete maschinelle Methoden.

5. Verschiedene charakteristische pulmonale Laesionen werden besprochen. Unter ihnen sind am auffälligsten die lokale Ansammlung von Fremdkörpern, die fokale Fibrose, die Nekrose der Zellen und des Grundgewebes, chronischer Makrophagen-Katarrh, Epithelialisierung der Alveolarwände, Granulombildung und Gefässschädigung.

6. Viele der beim Menschen beobachteten Veränderungen sind im Experiment ebenfalls erzeugt worden. Es war auch möglich, bei Ratten Lungenkrabs zu erzeugen durch Exposition mit verschiedenen Berylliumverbindungen selbst in sehr niedriger Dosierungsstufe.

7. Abgesehen von methodischer, experimenteller und klinischer Erforschung der vollen Wirkungsbereiche von Substanzen, denen der Mensch ausgesetzt sein kann, bleibt an Problemen noch zu lösen: die Schwellenwerte der Toxizität, besonders in Verbindung mit langer Exposition; die verschiedensten Reaktionen bei Tierarten und ihre Anwendbarkeit beim Menschen; präzise diagnostische Kriterien, besonders zu Lebzeiten; Gesundheitsgesetzgeberische Schwierigkeiten, die entstehen durch das verzögerte Auftreten der Erkrankung nach der Exposition und die nationale Bedeutung des Kernenergieprogrammes; Gegengifte und therapeutische Stoffe. Allein die weitere Forschung kann uns mit den notwendigen Antworten versehen.

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## The Program of the Atomic Energy Commission for Control of Inhalation Hazards of Nuclear Energy Operations\*

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Our Atomic Energy Program is one of the truly enormous enterprises of our national life, ranging from mining to computers and heavy industry to oceanography. Consequently, the total number and variety of industrial hazards is potentially large but, fortunately, most of them fall into the category of accepted industrial hazards and require no particular comment. However, when radiation and radioactivity become components of the overall process, each situation and operation must be individually re-evaluated and new industrial standards established as needed. This, of course, is standard procedure at all atomic energy projects, and as a result the AEC has been a partner to a remarkable advance in industrial hygiene and safety engineering techniques. Emphasis has been, and is, on the anticipation of hazards, followed by strict application of preventive measures and education of the worker. In many instances the design and operation of a plant or process has hinged on the recommendation of the health-safety groups. A very welcome by-product of this concern is the enviable industrial record of the AEC contractors.<sup>1</sup>

The lung features very prominently in all thinking and planning concerning possible exposure of personnel to both radioactive and non-radioactive agents. It is recognized as one of the more effective routes for introducing substances inside the body, considering that the alveolar ventilation in an average man amounts to nine kilograms or more of air per day. Whether foreign material in the inspired air will eventually reach the systemic blood depends on its particle size, solubility and some five additional minor properties.<sup>2</sup> In general, by the time the air reaches the larynx, particles larger than about five microns have been removed by the straining action of the vibrissae and by impaction on the moist mucous membranes of the upper respiratory tract; and similarly when the air reaches toward the finer bronchioles, the majority of the particles are one micron in diameter or less; the finest particles have been shown to reach the alveoli. If the larger particles are *insoluble*, they are removed mechanically by ciliary action and coughing. Particles brought up from the tracheobronchial system are for the most part swallowed; if they remain insoluble in the presence of the digestive fluids, their effect is negligible, but if they become soluble or chelated, they may be absorbed into the systemic circulation.<sup>3</sup>

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On the other hand, if the particles are directly *soluble* in body fluids, the substance can be absorbed through the alveolar membrane *into* the pulmonary capillaries and somewhat less readily across the nasal and bronchial mucosa. Some materials, such as coal, have surface properties which excite phagocytic action; these end up as deposits in the lymph spaces and lymph nodes.

Now where the processes have not involved radioactive materials, modern health-safety procedures and devices have been effective, although some of the compounds used in large amounts definitely are local irritants to the pulmonary tract; others possess toxic effects after having been absorbed into the systemic circulation.

The Atomic Energy Commission's concern with such conventional industrial hazards can be illustrated by the story of nickel carbonyl,  $\text{Ni}(\text{CO})_4$ , a compound used for catalysis and in preparing high purity nickel. It is both a pulmonary irritant and a systemic toxin. Since a vapor can never be fully contained in an industrial process, the operation was designed to maintain a concentration less than the accepted tolerance figure of one part per million. However, because it is a poorly understood chemical toxin, experimental research on the toxicology of the agent was instituted. The data from this project indicate that repeated pulmonary exposures of animals to concentrations of 20 and 40 parts per million lead to a state of chronic irritation of the respiratory tree with evidence of metaplastic changes. The overall findings support the presumed clinical association of this chemical with carcinoma of the respiratory passages,<sup>4, 5</sup> and justify the extra effort needed to maintain the tolerable environmental concentration. A by-product of the study is the development of an effective treatment for systemic nickel poisoning.

Dr. Schepers has described some of the research instituted in connection with the new metallurgical uses of large amounts of stable beryllium. This is typical of the studies on a number of other metals and chemicals, since we are turning more and more to the use of esoteric metals, alloys and chemicals for fabrication of the various types of reactors and their associated machines.

However, when radioactivity becomes a major component of the industrial hazard, every step of each process throughout the entire sequence must be re-examined and re-evaluated. Prior to 1942 the sum of our knowledge of radiation in relation to the industrial population was: 1) that radiation in sufficient amounts was tissue-destructive; 2) that the natural radioactive isotopes such as  $\text{Ra}^{226}$  could produce neoplasms in areas adjacent to where they localized in the body;<sup>6</sup> and 3) a strong suspicion that men who mined radioactive material had a higher than usual incidence of lung cancer.<sup>7</sup>

Many of the probable sources of radiation and radioactive contamination in the Manhattan Project were easily predicted, but many could not be; therefore, it is to the credit of the Project's medical group and engineers that they designed all operations for maximum anti-radiation protection. This philosophy still is a primary guide line. Nevertheless, there

was and is inherent in all atomic energy activities an element of possible exposure to external and internal sources of radiation. Some which are of current interest will be considered.

Much of the uranium ore in the United States is found in relatively circumscribed deposits in the arid Colorado Plateau and as a consequence, the working conditions inside the mines sometimes are less than optimal.<sup>8</sup> Concentrations of radon<sup>222</sup> or radium emanation, a daughter product of the radioactive decay of uranium, may reach concentrations as high as  $6 \times 10^{-8}$  curies/liter of air with averages around  $4 \times 10^{-9}$  curies/liter; the acceptable value of  $3 \times 10^{-10}$  curies/liter can be achieved in most mines, and proper ventilation of enclosed spaces such as laboratories or machine shops will keep the concentration of Rn to at least  $10^{-11}$  curies/liter, the permissible concentration recommended by the N.C.R.P.<sup>9</sup> A small fraction of this inspired radon gas will be absorbed into the tissues and before being exhaled, it will transform via its decay chain into Pb<sup>210</sup>, which will then deposit in the bone to exert the effects typical of radium. Other radon molecules will attach to whatever dust particles are present; these then behave like a radioactive form of that dust.

Uranium ore dusts are regarded like other relatively insoluble dusts except that limits of concentration in air have been established which are lower than those for simple silica dust atmospheres. The ore particle may have sufficient radioactivity to impress an appreciable radiation dosage on the underlying bronchotracheal mucosa as the particles are moved upward by ciliary action. A fraction of the ore dust, however, is soluble and is absorbed into the blood stream. The uranium ion, in contrast to Ra<sup>226</sup> or Pb<sup>210</sup>, tends to localize in the kidney;<sup>10</sup> thus the dosage to this organ ultimately determines the permissible environmental concentration. The occurrence of uranium in the urine is evidence of absorption from the lung, although a reliably useful relationship between the two has not yet been established.<sup>11</sup> And, finally, these mines provide a major silicosis problem, enough in some cases to cause a mine to be closed temporarily.

These same three problems also exist in varying degree in the crushing and concentration operations, but can be and are much better controlled. The mining and processing of thorium as a fuel for "breeder" reactors raises similar problems, but this element may be less hazardous from the industrial standpoint.<sup>12</sup>

These conditions are the object of considerable current research. A cooperative study has been developed between the United States Public Health Service, the State of Utah and the Atomic Energy Commission, which is designed to establish permissible standards for uranium mining techniques and ventilation, and simultaneously to evaluate these factors with respect to the health of the miners. Supporting this is a major continuation of experimental work in several AEC laboratories on the toxicology and radiotoxicity of uranium and thorium in the various forms relative to radium, strontium<sup>90</sup> and pure external gamma irradiation.

Separation of the uranium isotopes for enriched fuel and the production of fuel elements for reactors now are processes operated on a routine



manufacturing basis. Once this fuel begins to undergo fission, the type and design of reactor will largely determine the health hazard relative to the pulmonary portal. In the case of an air-cooled reactor, the inflowing air must be cleaned and dried to avoid neutron activation of dusts and foreign material; the discharged air nevertheless contains traces of active dusts plus radioactive krypton, xenon and argon created by the  $(n, \gamma)$  reaction with the stable nuclei of these noble gases. But by use of large volumes of air mixing in a tall stack, the activity is diluted to very low levels before being discharged. If, however, a fuel element fractures or leaks, the fission product mixes into the coolant air going up the stack. To control this contingency, numerous radioactive sampling devices are set to "scram" the reactor automatically whenever the concentration of radioactivity in the stack or in the environmental air exceeds predetermined, very low limits. Experience with the art of reactor operation now makes such scrams rare, but in any case the most that would happen is the beginning of a discharge of radioactive gases, some volatile radioactive isotopes, chiefly iodine and ruthenium tetroxide, and the dust-like effluvium of some 50 radioisotopes.<sup>13-16</sup> In reactors using a fluid fuel or a liquid coolant moderator, a power surge would result simply in a dispersion of the radioactive liquid but only within the shell or building enclosing the reactor.

During the chemical processing of spent fuel rods or liquid fuels fission products may get into the lungs. This separation process is highly developed and designed to operate by remote control so that ordinarily the pulmonary hazard is negligible; still there have been a few occasions when the system leaked or the stack became overloaded so that it was necessary to evacuate the immediate premises temporarily; however, in no case has the surrounding off-site countryside been affected. Because relatively large quantities of long-lived fission products are in these spent fuel rods, the Atomic Energy Commission has always insisted on the maximum degree of containment of the fission products; this policy has paid off many times.<sup>17</sup> Nevertheless, it is impossible to achieve absolute containment and workers occasionally may be exposed to small degrees of contamination which enter the body by way of the skin, wounds or abrasions, the gastrointestinal tract and/or the respiratory tract. Of most concern under these circumstance are  $\text{Pu}^{239}$ ,  $\text{Ru}^{106}$ ,  $\text{I}^{131}$ ,  $\text{Cs}^{137}$ ,  $\text{Sr}^{90}$ ,  $\text{Ba}^{140}$ , and perhaps tritium, or  $\text{H}^3$ ; these radioisotopes enter the respiratory tract as gases, as fine dusts, or as aerosols produced by entrainment in other emitted vapors.<sup>16,18</sup> Certain of these isotopes,  $\text{Cs}^{137}$ ,  $\text{Sr}^{90}$  and  $\text{Ru}^{106}$ , are of interest from the standpoint of long-term fallout from the stratosphere which enters the body via the food chain. Conversely, the immediate fallout from a nearby burst could create a dust problem for the lung, but the particles are comparatively large.<sup>19, 20</sup>

Some of the very first fission product from the Manhattan Project was set aside for biological studies, because the problem of contamination of personnel was recognized to be a primary limiting factor in all operations. The late Dr. Joseph Hamilton of the Crocker Laboratory, University of California, set up the screening program which provided the ini-

tial information on these new radioisotopes; these data were then used to establish the permissible limits and concentrations. This type of work has expanded to the point that a considerable part of the total effort of the Division of Biology and Medicine of the AEC is directed toward obtaining data which can be used to compute the maximal permissible values found in the National Bureau of Standards Handbook No. 52.<sup>9</sup> This handbook, incidentally, will soon be revised using recently accumulated data including an appreciable amount on man himself.

The containment and disposal of radioactive wastes should never create problems relative to the lung because it is under engineering control.<sup>18, 21</sup> However, if a container were to leak or break during transportation to a storage area, the spill could become a source of dusts and aerosols.

The chronic effects of penetrating gamma or x-radiation on the lung are to cause fibrosis and perhaps to act as a carcinogen,<sup>22</sup> but because the lung is grouped with the radio-resistant tissues, one ought to find similar but more lethal damage in tissues such as bone marrow occurring before the fibrosis is able to show itself.

The simple passage of a dilute soluble radioactive aerosol or gas across the lung membranes would not be of much significance to the lung unless the lungs were filled with a very high concentration of it. This, however, may be of practical significance now that krypton<sup>85</sup> and tritium are available in large amounts of very high specific activity. It has been calculated, for instance, that a single deep breath of pure tritium would give a surface dose to the lung tissue of about 4000 rep per second. More dangerous, however, would be the inhalation of the gaseous form of nearly pure T<sub>2</sub>O: In the extreme case, a three-second inhalation of gaseous T<sub>2</sub>O would result in an integrated total body dose of between 3,000 to 10,000 rep;<sup>23</sup> on the other hand, a continuous concentration of  $5 \times 10^{-6}$   $\mu$ c of tritium/ml. of air is estimated to result in the tolerance 0.3 rem per week.<sup>24</sup>

Inhalation of an aerosol which is insoluble in the body fluids presents a different hazard. In the case of plutonium oxide, only a small amount dissolves in the blood; this then is deposited rather firmly in the bone. The remainder moves up the respiratory tract and into the gut, as particles with at least two different half-times of removal, one of about six months and one of a few weeks.<sup>25</sup> Pu<sup>239</sup> emits  $\alpha$ -particles as it decays; these  $\alpha$ -particles impose a highly concentrated dose of radiation to the underlying tissue so that a narrow streak of dead or damaged mucosa will be left behind as the particle moves upward. There are large numbers of such particles continuously moving up the same course, giving essentially repetitive radiation which may be especially carcinogenic. In any case this continual radiation dose to the mucosa may be ultimately more damaging than that to the alveoli.

Methods of treating persons with internal contamination are most effective for those radioactive isotopes which have the least tendency to localize in tissues and are most soluble. One attempts as quickly as possible to chelate the absorbed isotope and divert it out the excretory routes. To this end, one gram dose of calcium disodium ethylenediaminetetra-acetic



acid are injected intravenously once or twice a day for one to four days. In addition, diuretics, renal acidifying agents, and saline cathartics may be used to magnify the excretory activity. For radioisotopes such as  $\text{As}^{74}$  or  $\text{Hg}^{203}$ , British antilewisite (dimercaptopropanol) would be preferred to the above EDTA.

In the case of contamination by plutonium, a single dose of zirconium citrate (25 mg. Kg. body weight) is injected intravenously as quickly as possible in order to saturate the surfaces of the body tissues onto which the plutonium ion would localize. Radioisotopes such as those of  $\text{Na}^+$ ,  $\text{H}^+$  and  $\text{I}^-$  can be most effectively eliminated by giving large amounts of the stable isotope combined with diuresis; by this means the stable isotope dilutes the radioactive form, competes more effectively with it for the available metabolic reactions, and finally carries the radioisotope out of the body when the excess ion is excreted as the homeostatic mechanisms come into play.

The insoluble isotope must be removed mechanically. If the contamination is under the surface, the area is excised. Simple debridement is rarely sufficient to remove the radioisotope since less than milligram amounts remaining in a wound may provide a potentially lethal body burden; occasionally amputation may be warranted.

Rinsing the nasal passages and irrigation of the upper respiratory tract should be carried out as quickly as possible. Unfortunately, nothing effective can now be done to promote more rapid clearance of particles from the lung; this is a point for research. If most of the activity were shown to be localized in one lobe of the lung, lobectomy probably would be indicated.

#### SUMMARY

The Atomic Energy Commission's broad activities bring it into contact with many situations and compounds which affect the lungs. Most of them, fortunately, are familiar industrial problems for which there are acceptable solutions. Superimposing radiation, however, has necessitated major research and development efforts aimed at controlling contamination and the effects of radiation. Up to now, the record indicates we have been reasonably successful and certainly it is one of the few instances of a major industry making a primary effort in health protection without it being obliged to do so because a series of major accidents took place.

#### RESUMEN

Las amplias actividades de la Comisión de Energía Atómica la llevan al contacto con muchas situaciones y compuestos que afectan los pulmones. Afortunadamente la mayoría son problemas industriales a los que se han familiarizado y para los cuales hay soluciones aceptables.

La radiación reiterada sin embargo, ha necesitado investigación mayor y el desarrollo de esfuerzos encaminados al control de la contaminación y de los efectos de la radiación. Hasta ahora la observación indica que hemos tenido razonable éxito y ciertamente ésta es una de las pocas ocasiones en

que una gran industria hace un esfuerzo desde el principio par proteger la salud sin verse obligada a ello a causa de la ocurrencia de accidentes grandes.

#### ZUSAMMENFASSUNG

Die umfangreiche Regsamkeit der Atomenergierkommission bringt diese in Kontakt mit vielen Stellen und Verbindungen, die die Lunge betreffen. Die meisten von ihnen stellen glücklicherweise bekannte Industrielle Probleme dar, für die sie annehmbare Lösungen bedeuten.

Die zusätzliche Bestrahlung hat jedoch grössere Untersuchungen erfordert und die Entwicklung von Bemühungen mit dem Ziel der Beherrschung der Abfallstoffe und der Wirkungen der Bestrahlung. Bis jetzt erweisen die Aufzeichnungen, dass wir ziemlich erfolgreich waren, und sicher ist dies eine der wenigen Gelegenheiten, bei denen ein grosser Industriezweig eine primäre Anstrengung unternimmt zum Schutz der Gesundheit, ohne dazu verpflichtet zu sein, weil eine Reihe von grösseren Unfällen erfolgte.

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## The Public Health Aspect of Nuclear Energy, With Particular Reference to Inhalation Hazards and to Diseases of the Chest\*

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"The public health aspect of nuclear energy" is, without doubt, the most formidable phrase that any medical man was ever requested to include in the title of his address. Since a certain summer day 12 years ago the entire population of the globe has stood face to face with the unprecedented problem these words express. Our "public" in this sense includes every human being on earth. The best brains in the world have struggled with the problem for more than a decade and, as the newspapers and magazines assure us with ever increasing stridency, have reached no agreement, even on definition of terms.

This, gentlemen, is a discussion topic that even a Washington official finds himself approaching with something less than that occupational self-confidence of which we are, from time to time, accused.

Often, however, a new job turns out, upon examination, to contain familiar elements, and the rather staggering nature of many new assignments begins to cause less apprehension when we discern that many of the components are customary, standard procedures with which we have worked for a long time.

The dawn of the atomic age, and the health hazards inescapably associated with the use of nuclear energy, may appear to present the public health profession with its newest responsibility, but in truth this energy-revolution simply renders more dramatic, and perhaps more urgent, the basic responsibility which is as old as the public health movement—the responsibility for creating and guarding a safe environment in which man can live and in which man can work. Many traditional public health disciplines—I am thinking of sanitary engineering, medical research, and industrial health—have over the years perfected the tools and provided the training for public health workers who must, in the decades ahead, solve the new problems that will grow with each step we take into this atomic age.

Before discussing what the public health profession can do—and is doing—about potential radiation hazards, it may be useful to distinguish, as we do in the field of air pollution, between the acute and chronic effects of exposure. Only where a serious accident occurs, caused by large radiation exposures, can acute effects be anticipated. The symp-

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toms will appear within a few days or weeks and should be immediately recognizable. Chronic low-level radiation exposure is at the present time the more important public health problem (again, there is an analogy with air pollution).

What are the principal sources of radiation exposure?

From the public health point of view the wartime, and subsequent military employment of atomic energy is only one of several sources of total population exposure to radiation.

The testing of bombs, and other developments connected with the military use of atomic energy, have caused international debate over atomic health hazards to reach new heights in recent months; and the interest of the Public Health Service in protection methods in uranium mining was accelerated by wartime activities. There are, however, three chief sources of radiation exposure that constitute the purely civilian aspect of this problem. I have in mind first, the type of exposure which is related to the peacetime atomic energy industry; second, the exposure which results from the presence of natural radioactive substances in the environment and from cosmic rays; and third, exposure encountered in the healing arts, especially in x-ray procedures.

The European project for the international development of atomic power for industry (Euratom) will, it is expected, contribute to the expansion of atomic industry in this country during the next decade, although the American need for a new source of industrial power is far less urgent than the European requirement. Both the workers in the atomic-fueled plants of the future and the general population must be protected from various types of radiation hazard (including the dangers inherent in the disposal of radioactive wastes). Few public health assignments will have a higher priority when we reach the stage where nuclear energy has become a serious rival to coal and oil as a principal support of American industrial strength. The techniques of industrial or occupational health will also at that time be tested to the utmost.

The second source of radiation exposure—radioactive substances in the environment and cosmic rays—is for the most part beyond man's control. We are all exposed to a natural background of radiation, compounded of cosmic radiation (and its secondary radioactivity), the radioactive elements present in the earth (radium and radioactive potassium, for example), and even a minute proportion of certain of the elements present in the human body itself. This natural background is not uniform throughout the world, nor in all parts of this country. At higher altitudes the contribution of cosmic radiation increases, and, of course, there is an uneven distribution of the deposits of radioactive elements in the earth.

The sum total of natural sources of radiation—over which we can exercise little control—is generally regarded by experts at the present time as constituting the second largest single source of radiation exposure with which we are confronted. The largest source is that related to the healing arts. The danger of overexposure of x-ray operators, other medi-



cal personnel, and patients themselves is a direct challenge to public health, and a challenge to which we have responded.

The first reported case of human injury from radiation came only a few months after publication of Roentgen's original paper (1895) announcing the discovery of x-rays, and during the following decade many of the now familiar acute and chronic radiation effects were observed and reported.

The principal chronic effects of radiation are understood today to be (1) reduction of the life span, (2) production of genetic mutations, and (3) increased incidence of cancer. For example, an increase in leukemia and other neoplasms, as well as an increase in the number of congenital abnormalities in the offspring of radiologists, as compared with other medical specialists has been reported.

At the present time it is estimated that some 250,000 individuals in this country are engaged in the operation of about 125,000 medical and dental x-ray and fluoroscopic units. This total includes physicians, dentists, veterinarians, nurses, and others.

Since medical and dental uses form the largest single source of radiation exposure, the potential hazard to the patient must in each individual case be carefully balanced against the potential life-saving gain that may be realized through the employment of x-rays. The decision in each case must be made, of course, by the individual physician or dentist, since he alone can make a personal evaluation of all pertinent factors in the case.

While the traditional patient-physician relationship is seldom more dramatically justified than under these circumstances, research progress in recent years emphasizes the need for taking into consideration a vital non-personal factor. By this I mean that personal exposures that might have been acceptable in the absence of any other environmental exposure should now be re-evaluated in the light of current knowledge concerning the *total and potential radiation exposure of the entire population from all sources*.

The ultimate responsibility for the establishment and enforcement of uniform radiation health standards remains with State and local health agencies, in accordance with the American tradition of local self-government, but the Federal contribution in this field can be as effective as in other areas of public health.

Broad environmental control activities have been prominent features of the work of the Public Health Service in radiological health thus far, but we are moving into a period of increased emphasis on the medical aspects of control of radiation hazards. Existing training programs developed by the Service to increase the competency of health agency personnel in the environmental field will be supplemented by short courses designed to meet the needs of health agency medical personnel. The accompanying expansion of State and local training programs of a similar nature will be encouraged.

In addition to training, research and the dissemination of information



are standard Public Health Service operations. The need for epidemiological research in the quantitative aspects of low-level radiation hazards is an urgent one. Only through epidemiological studies of sizeable populations with known exposure to radiation can we secure the data required for determining maximum permissible exposure levels accurately. At the present time wide variations in exposure are reported, even within the same groups. For example, recent studies have indicated that, among x-ray practitioners, exposure varies from none at all to a figure in excess of the current "permissible" rate.

Techniques are available for reducing the exposure resulting from x-ray and fluoroscopic machines without adversely affecting (and, in some cases, with an actual improvement of) the diagnostic quality of the results. Wider dissemination of information concerning these techniques can be achieved by public health workers in close cooperation with the medical profession. Health officers, engineers, public health nurses, health educators, and other categories of public health personnel can all play a useful role in this cooperative educational effort.

A major activity of the Public Health Service in the special field of inhalation hazards and diseases of the chest has been the work carried on in the uranium mining industry.

The European experience in this connection is important. For 500 years mining operations have been carried on in the Erz Mountains of Czechoslovakia and Bohemia and, after the discovery of radium, pitchblende in these mines was exploited for its radium content. For centuries writers have noted the high mortality from pulmonary diseases among miners in this area, and toward the end of the 19th century investigators identified the affliction as a malignant tumor of the lungs. Some medical reports attributed to primary cancer of the respiratory system as high a proportion as from one-half to three-quarters of all deaths among workers in these mines, and currently the predominant opinion is that radioactivity in the mines has been responsible for the situation.

While it was recognized that European and American mines are in many ways not comparable, it was natural for public health agencies to become seriously concerned over the potential health problem represented by the beginning of uranium production on a large scale in the United States. Although our mines are more shallow than those in the Erz Mountains, and yield a less complex ore, while our miners seldom work underground more than 40 hours a week, still early environmental studies in American uranium mines had revealed considerable concentrations of radioactive gases and dust.

The Public Health Service, therefore, initiated research into the problem of adequate control measures for the mines and undertook, in cooperation with State health departments and the industry, a series of periodic physical examinations of the miners.

What happens in a uranium ore body is that uranium 238 very slowly, and through successive transformations, is converted to radium 226 which, in turn, disintegrates into radon, a radioactive gas about seven times

as dense as air. Radon is diffused from the ore and is released by drilling and blasting operations, becoming dispersed throughout the mine atmosphere. Also, within several days, radon itself breaks down into radium A. Radium A and subsequent transmutation products are called radon "daughters."

The daughter products tend to adhere to dust particles, because of their electrostatic charge, and they thus enter the respiratory system in two ways—through inhalation of radon gas and through inhalation of dust particles in the mine atmosphere.

The work of the Public Health Service has demonstrated that, through proper ventilation of uranium mines, the concentration of radon and its daughter products can be reduced to a recommended level, and the lungs of uranium miners can be protected from radioactive gases and dust. Physical examinations of 2,000 uranium miners have been carried out 3 times since 1950, and have been supplemented by an annual census and followup of the miners, in an effort to determine whether there has been health damage to workers in uranium mines in the United States that might be attributed to radiation.

It has been emphasized that the establishment of adequate control measures, such as ventilation, should not be delayed, since by the time biologic damage becomes clinically detectable it may be unresponsive to medical therapy. The latent period for development of lung cancers in European miners was from 10 to 17 years. According to 1956 Census records there are 65 miners with over 10 years of experience in American uranium mines.

The application of industrial health principles, and of occupational health experience such as that gained in work with silicosis over the years, has contributed to the solution of inhalation hazards in uranium mining. It likewise illustrates the applicability, which I mentioned earlier, of traditional public health tools and procedures to this great new health problem area of nuclear energy.

We believe that we have the tools to cope with this problem of exposure of our population to radiation from many sources.

The task ahead is one of organization, research, and application.

#### SUMMARY

The dawn of the atomic age, and the health hazards inescapably associated with the use of nuclear energy, presents the Public Health Service with its newest responsibility.

We must distinguish in radiation health hazards, as we do in the field of air pollution, between the acute and chronic effects of exposure. Only when an accident occurs, caused by very large radiation exposure can acute effects be anticipated. The symptoms will appear within a short time and should be immediately recognizable.

There are three chief sources of radiation exposure that constitute the purely civilian aspect of this problem. First, the type of exposure that is related to peace-time atomic energy. Second, the exposure which re-

sults from the presence of natural radioactive substances in the environment and from cosmic rays. Third, exposure encountered in the healing arts, especially x-ray procedures.

Workers in the atomic-fueled plants of the future, and the general population must be protected from various types of radiation hazards (including the dangers inherent in the disposal of radioactive waste). Radioactive substances in the environment and cosmic rays, are for the most part, beyond man's control. The danger of over-exposure of x-ray operators, other medical personnel and patients themselves is a direct challenge to public health, and a challenge to which we have responded.

The principal chronic effects of radiation are understood today to be reduction of life span, production of genetic mutations, and increased evidence of cancer. At the present time some 250,000 individuals in this country are engaged in the operation of about 125,000 medical and dental x-ray and fluoroscopic units.

Techniques are available for reducing the exposure resulting from x-ray and fluoroscopic machines without adversely affecting the diagnostic quality of the results.

Health officers, engineers, public health nurses, health educators, all play a role in a cooperative educational program.

A major activity of Public Health Service in the special field of inhalation hazards and disease of the chest has been the work carried on in the uranium mining industry. The Service has demonstrated that through proper ventilation of uranium mines, the concentration of radon, and its daughter products can be reduced to recommended levels and the lungs of uranium miners can be protected from radioactive gases and dust.

#### RESUMEN

La aurora de la edad atómica y los peligros a la salud forzosamente asociados al uso de la energía atómica, presentan a los Servicios de Salubridad Pública nuevas responsabilidades.

Debemos distinguir en los peligros de la radiación para la salud, como lo hacemos en el campo de la polución del aire, entre los efectos agudos y los crónicos de la exposición. Los efectos agudos pueden esperarse sólo cuando ocurre un accidente causado por una gran exposición a la radiación. Los síntomas en este caso aparecerán pronto y deben ser reconocibles inmediatamente.

Hay tres fuentes principales de exposición que constituyen el aspecto civil del problema. Primero: el relacionado con el uso de energía atómica en tiempo de paz. Segundo la exposición resultante de las sustancias radioactivas en el medio circundante y, Tercero: la exposición que se encuentra en el arte de curar especialmente por los rayos X.

Los trabajadores en las plantas de combustible atómico del futuro, y la población general, debe protegerse de las varias formas de la radiación (incluyendo los peligros que corresponden a los materiales radioactivos de desecho). Las sustancias radioactivas en el medio circundante y los

rayos cósmicos, son en su mayoría incontrolables por el hombre. El peligro de sobre-exposición de los operadores de rayos X, otro personal médico y los mismos enfermos constituyen un desafío a la salubridad pública, un desafío al cual hemos respondido.

Los efectos crónicos de la radiación se comprenden ahora como un acortamiento de la duración de la vida, producción de cambios genéticos y una mayor frecuencia del cáncer. Actualmente alrededor de 250.000 personas este País trabajan en 125.000 unidades de rayos X médicas y dentales.

Existen técnicas para reducir la exposición a los rayos X y a la fluoroscopia sin dañar a la calidad del trabajo.

Los empleados de salubridad, ingenieros, enfermeras de salubridad, educadores sanitarios, todos, desempeñan un papel en el programa educacional cooperativo.

Una actividad importante de los servicios de salubridad pública en el campo de los peligros de la inhalación y enfermedades del pecho se ha desarrollado en la industria de las minas de uranio.

El servicio ha demostrado que por medio de una ventilación adecuada de las minas de uranio, la concentración del radón y de sus productos puede reducirse a los niveles recomendados y los pulmones de los mineros de uranio pueden protegerse de los gases y polvos radioactivos.

#### ZUSAMMENFASSUNG

Der Anbruch des Atomzeitalters und die unmittelbar mit der Verwendung von Kernenergie verknüpften Gesundheitsschädigungen bescheren dem öffentlichen Gesundheitswesen seine jüngste Verantwortung.

Bei den gesundheitlichen Strahlenschädigungen müssen wir, wie wir es auch auf dem Gebiet der Luftverunreinigung tun, unterscheiden zwischen den akuten und den chronischen Wirkungen der Exposition. Nur wenn ein Unfall eintritt, der durch eine sehr ergebnisreiche Strahlen-Exposition verursacht wird, können akute Wirkungen erwartet werden. Die Symptome werden innerhalb kurzer Zeit erscheinen und müssen unmittelbar erkennbar sein.

Es gibt 3 Hauptquellen der Strahlen-Exposition, die die rein zivile Seite dieses Problems bilden: zum ersten den Typ der Exposition, der verknüpft ist mit der friedlichen Atomenergie. Zum zweiten die Exposition, die sich ergibt aus der Gegenwart von natürlich radioaktiven Substanzen in der Umwelt und von kosmischen Strahlen. Zum dritten die Bestrahlung, der man in der Heilkunde begegnet, vor allen den Röntgenstrahlen.

Es müssen die Arbeiter in den mit Atomkraft betriebenen Werkanlagen der Zukunft und die gesamte Bevölkerung geschützt werden vor den verschiedenen Typen von Strahlenschädigungen (einschl. der Gefahren, die mit der Beseitigung von radioaktiven Abfällen verknüpft sind). Radioaktive Substanzen in der Umwelt und die kosmischen Strahlen liegen zum grössten Teil jenseits der menschlichen Kontrolle. Die Gefahr der Strahlen-Überdosierung bei den mit Röntgenstrahlen Beschäftigten und anderem medizinischen Personal und bei den Kranken selbst ist ein unmittelbares

Anliegen des öffentlichen Gesundheitswesens und ein Anliegen, dem wir entsprochen haben.

Unter den hauptsächlich chronischen Wirkungen der Bestrahlung versteht man heute die Herabsetzung der Lebensdauer, das Entstehen von Gen-Mutationen und das zunehmende Auftreten von Krebs. Im gegenwärtigen Zeitpunkt sind ungefähr 250,000 Personen in den Vereinigten Staaten beschäftigt mit der Handhabung von etwa 125,000 ärztlichen und zahnärztlichen Röntgenaufnahme und Durchleuchtungsgeräten.

Es stehen Methoden zur Verfügung zur Verringerung der Strahlen-Exposition, die bei den Röntgenaufnahme- und Durchleuchtungsgeräten vorkommt, ohne die diagnostischen Qualitäten der Befund ungünstig zu beeinflussen.

Gesundheitspfleger, Techniker, Fürsorgerinnen, Gesundheitslehrer, sie alle spielen eine Rolle im gemeinschaftlichen Erziehungsprogramm.

Von grosser Wirksamkeit für das öffentliche Gesundheitswesen auf dem besonderen Gebiet der Unfälle durch Inhalation und Thoraxerkrankungen war die in der Uran gewinnenden Industrie entfaltete Tätigkeit. Die hier ausgeführten Arbeiten haben bewiesen, dass durch entsprechende Belüftung der Urangruben die Konzentration von Radium-Emanation und ihrer Tochterprodukte auf zulässige Höhen herabgesetzt und die Lungen von Uran-bergleuten vor radioaktiven Gasen und Staub geschützt werden können.



## Early Diagnosis and Treatment of Tuberculosis in Children\*

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For the early diagnosis of tuberculosis in children, routine tuberculin testing and a careful and detailed history are of prime importance. A careful physical examination should also be done although in the early primary infection it most likely will be entirely negative. Chest x-ray films are not as specific as is the tuberculin test but they are more specific than the symptoms, and they are very important. It is difficult to obtain a definitive x-ray film on a squirming child but it is impossible to make a diagnosis on a poor film. An apparently negative film does not rule out active tuberculosis, especially in the tuberculin-converter with recent heavy tuberculosis exposure. Miliary and meningitis develop in some babies whose films showed little or no evidence of a primary complex. Calcium deposits sometimes appear later in serial x-ray films at the site where only equivocal soft shadows were visible on the first films. After the 9 per cent miliary cases and the 2 per cent reinfection pulmonary cases are excluded the incidence of initial positive gastric cultures among the remaining 89 per cent of the in-sanatorium children is about 27 per cent. Positive gastrics are not uncommonly associated with these equivocal shadows.

The fact that primary tuberculosis lesions may be hidden in the routine x-ray film by the heart, mediastinal structures, large vessels or the diaphragm is well known. Dr. J. A. Myers reports that comparison of antemortem chest films and autopsy findings show that posteroanterior films of the chest fail to reveal 90 to 95 per cent of recent primary lesions and 70 to 90 per cent of long standing primary lesions. Dr. Henry Sweany found at autopsy that 31 per cent of pulmonary lesions were so located that they were obscured in the posteroanterior chest films. In addition 10 to 15 per cent of tuberculosis lesions are extrapulmonary and would, therefore, be missed by the routine chest film. These facts must be kept in mind when evaluating any case from the standpoint of tuberculosis. Histoplasmosis may cause either the primary type or miliary type lesions in the lungs: foreign bodies in a bronchus may cause lesions resembling those of the atelectasis distal to bronchial obstructive types of primary tuberculosis and not infrequently the roentgenologist's report concludes with "please repeat x-ray film in two weeks to rule out pneumonia."

In taking the history one must remember that dates in children are of considerably more importance than in adults; e.g., date of babyhood and of puberty, date of beginning and end of contact with "open" tuberculosis,

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\*\*William H. Maybury Sanatorium.



date of onset and of duration of symptoms, date of negative and of positive tuberculin reaction, date of BCG inoculation (if any) and date of negative and of positive x-ray findings. The effort used in obtaining this information will be fully justified.

Since January 1, 1956, 335 children from the Detroit area have been treated in Maybury Sanatorium; 98 per cent of them had a positive tuberculin test and 85 per cent of them had x-ray film evidence of primary tuberculosis in the lungs although 35 per cent of them had other tuberculosis.

A review of these 335 cases shows that almost three-quarters of them had the onset of tuberculosis before five years of age. This certainly indicates that tuberculin testing should be done routinely in well-baby clinics, doctors' offices, and hospitals as part of the examination of all children and not left to the surveys of children of school age.

In detail the age of onset of tuberculosis in the pre-school group was found to be as follows: under one year of age 17.9 per cent, one year 21.8 per cent, two years 15.5 per cent, three years 8.4 per cent, four years 8.9 per cent. The earliest onset was at five weeks of age and she was admitted to the sanatorium at two and one-half months of age in a state of shock. She was drowning in bronchial secretions which were already positive for tubercle bacilli. The fact that a greater proportion of these infected babies will early develop serious and stormy symptoms makes them sensitive and accurate clinical barometers of "open" tuberculosis in the home.

The age of onset was five to eight years inclusive in 21.8 per cent of the children. This would indicate that their resistance to the development of clinical tuberculosis is only slightly less in relation to babies and to pre-

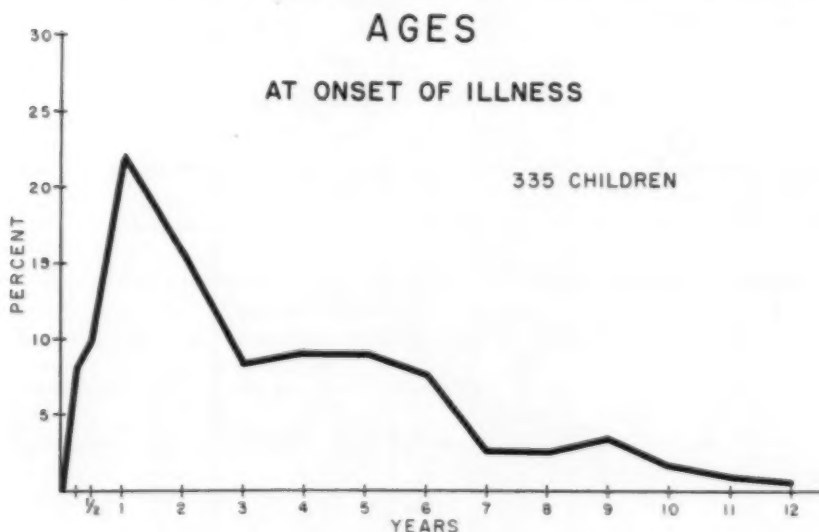


FIGURE 1

# SOURCES OF CONTACT

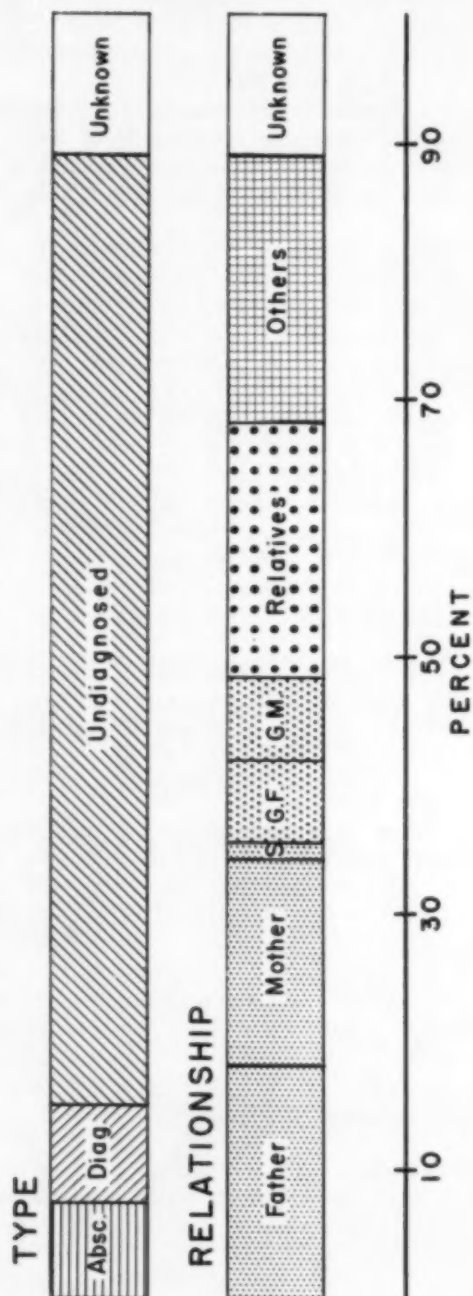


FIGURE 2

adolescents or adolescents and that their age should not preclude the use of specific therapy as soon as fresh active tuberculosis is discovered.

The age of onset was nine to twelve years inclusive in 5.7 per cent of the children. Our upper limit of admission age is the 12th birthday. Over two-thirds of the children having onset at nine to twelve years were pre-adolescent Negro girls; while the remainder were boys who were not yet pre-adolescent and had the same ethnic distribution as the whole population of the Maybury Sanatorium Children's Division, i.e., 40 per cent white and 60 per cent Negro.

Further analysis of these 335 children emphasizes the need for better education, cooperation, and control of the adult with active tuberculosis. When an "open" case of tuberculosis is found, an attempt should be made to estimate the duration of this adult's infectivity. Then a careful history should be obtained as to all the places where and all the persons with whom he lived during that time. It is not enough to check just the present household.

About 74 per cent of the children were infected by adults who had not previously been diagnosed as having tuberculosis: More than 15 per cent were infected by persons who were known to have tuberculosis (7.4 per cent had absconded from sanatoria, 7.8 per cent had had a previous sanatorium admission or an x-ray film diagnosis in a survey unit, selective service, employment, a clinic, or a doctor's office). The source of contact was not found for 11 per cent of the cases.

The source of contact as to immediate family, other relatives, and non-relatives is as follows; roughly 16 per cent of the children were infected by mothers, 18 per cent by fathers, one per cent by siblings, seven per cent by grandmothers, six per cent by grandfathers, eight per cent by aunts, 10 per cent by uncles, two per cent by cousins and 21 per cent

### SYMPTOMS vs DIAGNOSIS

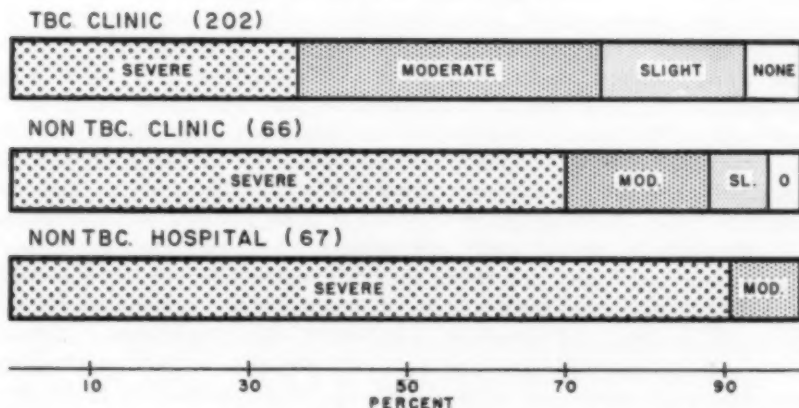


FIGURE 3

by non-relatives who consisted almost entirely of lodgers and of friends who came to visit or were visited frequently. The infections were all in home areas except one nine-year-old girl who contracted it from a 10-year-old classmate with advanced tuberculosis.

Symptoms of tuberculosis in children are variable and not specific, but they indicate that the child is not well and, therefore, are important. Of the above mentioned 335 Maybury-treated children 5.6 per cent were without symptoms both on history of present illness and on observation at the time of admission. The other 94.6 per cent had symptoms ranging all the way from a comatose state of meningitis to irritableness accredited prior to admission to such factors as teething and to lonesomeness for the mother who had gone to the sanatorium or had taken a job. The degree of symptoms experienced during the present illness had some correlation with where the diagnosis was made.

Of the 67 children having a diagnosis of tuberculosis made during a non-tuberculosis hospital admission, 91 per cent had severe and 9 per cent had moderate symptoms. When the diagnosis was made on 66 of the children in a non-tuberculosis clinic or doctor's office, 69.7 per cent had severe, 18.2 per cent moderate, 7.7 per cent slight, and 4.5 per cent had no symptom but were found on routine tuberculin testing. When the diagnosis was made on 202 children in the tuberculosis clinic, 36.1 per cent had severe, 37.6 per cent moderate, 18.4 per cent slight, and 7.9 per cent had no symptom. Most of the children who had been in the non-tuberculosis hospital and many of those in both clinic groups had had high fever and had initially received treatment for suspected pneumonia. Some of the tuberculosis clinic group had been treated in non-tuberculosis hospitals and clinics during the present illness before being checked as tuberculosis contacts. It is disturbing that a large number were treated in non-tuberculosis hospitals and non-tuberculosis clinics after having had a checkup as tuberculosis contacts, i.e., after having been identified as a potential case of tuberculosis. Of the 335 children there were 71 (21 per cent), admitted to the sanatorium who were being carried as "observation" cases subsequent to the contact checkup for tuberculosis. Of these children, 19 had negative tuberculin, being in the incubation period of tuberculous infection; seven had had negative tuberculin on the first checkup and positive later but were nevertheless continued on further observation; 38 had positive tuberculin at first contact checkup but it was apparently not considered to be significant and seven had an equivocal tuberculin reaction at the first checkup (in four cases the tuberculin test was not properly done, one did not return for a reading, one developed a generalized rash which confused the picture, and one had had BCG). Of these 71 children, the interval between their being placed on observation and their admission to the sanatorium was one to 12 months in 61 cases and one year or longer in 10 cases. In most of these cases between three and nine months delay in making the diagnosis had been permitted. The degree of symptoms during their present illness was severe in 35 children, moderate in 25, slight in eight, and

there was no symptom in three children. Symptoms did not always coincide with extent of tuberculosis; for instance, two children with miliary disease had only slight symptoms.

Among these 71 children the most serious tuberculous lesions which had developed were 10 cases of miliary and/or meningitis and one case of advanced pulmonary tuberculosis. One of the meningitis cases had had a positive tuberculin reaction two years earlier. In an 11-year-old girl who had miliary tuberculosis and recent tuberculosis of the wrist, the tuberculin conversion had occurred in babyhood. In a 10-year-old girl with acute fulminating advanced pulmonary tuberculosis who required subsequent left upper lobe resection, the first contact checkup at two years of age had been negative but three months later the tuberculin was positive.

From the standpoint of drug efficacy, the most opportune time to treat tuberculosis is when the infection is fresh, active, and small.

Admittedly a large proportion of infected children will not develop clinical tuberculosis and for these the use of antituberculosis therapy following infection is unimportant but for those children who will develop progressive tuberculosis the use of INH and PAS at the time the infection is discovered is mandatory. In order to protect the few from progressive tuberculosis we must treat all the potential cases. Using drug therapy in the fresh small tuberculous lesion, even those not yet detectable, seems to us much more definitive than does withholding it for use in case the primary and/or extrapulmonary lesions progress and become more caseous and more walled off.

One never really feels safe in discontinuing therapy which is initiated for old—but still active—primary tuberculosis especially if associated with meningitis, tuberculoma of the brain or other extrapulmonary lesions. Compared with the fresh, small lesions, these old ones have a greater potentiality for causing drug resistance and for requiring future treatment.

It seems to us that it is not a problem as to whether or not to initiate specific therapy on the children with fresh, active tuberculosis but rather how to be able to start all such children without delay and to assure that the prolonged continuous course will be carried through to completion.

For the recent tuberculin converter with little or no x-ray film findings we would start isoniazid with 7 or 6 mg./Kg. per day divided into two doses and PAS 150-100 mg./Kg./day divided into three doses. The dosage would later be reduced to 5 mg./Kg. before the end of the year's treatment. Since we have been adding PAS to the isoniazid in cases having small visible lesions it seems indicated in invisible lesions also.

Isoniazid must be one of the drugs given to children. It is the most effective against meningitis. Five to 3 mg./Kg./day are effective in some cases but in those which happen to be rapid acetylators larger doses are indicated and  $B_6$  could be given. Rarely does a child have intolerance to

isoniazid. In the sanatorium our actual intolerance to PAS is low and its acceptance is a part of the sanatorium routine.

The recent tuberculin converter does not have stable lesions regardless of the degree of symptoms and signs. Therefore he should be started on INH-PAS and on a routine which will maintain him in an optimum state of health. He should have adequate diet with supplemental vitamins and special attention to nitrogen and calcium balance. He should be protected from colds, childhood diseases and intercurrent infections. Fatigue should be prevented. The amount of bed rest will depend on the symptoms and x-ray film findings. In the beginning some will need bed rest for the first few months. All should have at least a lying-down rest period in the morning, a sleeping rest period right after lunch and should go to sleep early at night. When any exercise is allowed a good portion of it should be designated for regular daily short periods of quiet play outside. If of that age, school should be allowed after a few months for the child who from the beginning was free of symptoms and x-ray film finding. A rest period should be taken when he returns from school.

A heavily exposed, tuberculin-positive baby should be given Isoniazid and PAS at once regardless of symptoms: We cannot justify waiting for an acute illness or confirmatory x-ray film findings before starting therapy. He more urgently needs treatment if he has x-ray findings which suggest "pneumonia" and particularly if he has acute symptoms of "pneumonia." We must not wait for culture reports but start antituberculosis and broad spectrum antibiotic therapy as soon as throat swabs, gastric washings and, if indicated, spinal fluid specimens are obtained. Should complete investigation rule out tuberculosis the antituberculosis drugs would be discontinued and no harm would have been done. However, if antituberculosis drugs are not used promptly and the child develops meningitis, miliary or some other form of serious progressive tuberculosis there would be no returning to the early advantageous starting point.

Experience with children who have run the gantlet from tuberculosis exposure through periods of neglect, "observation" misdiagnosis and delay tends to crystallize several points in recommending the procedure in handling such cases.

Since the tuberculin test is the most specific of all procedures and can detect tuberculosis whether or not there are symptoms and other findings, it should carry the most weight in making an early diagnosis of tuberculosis in children. In order for a positive tuberculin test to represent active tuberculosis it must be supported in some of the following ways: (a) by a recently dated previous negative tuberculin reaction, (b) by the associated symptoms and/or x-ray evidence of active tuberculosis, (c) by the demonstration of tubercle bacilli in collected specimens, (d) by finding among the close associates an "open" case of tuberculosis of recent origin, or (e) by the young age of the child. Certainly if the child is under one year of age the disease could be considered as active and as probably active if the child is two or even three years of age but in a six-year-old child, age would definitely *not* be confirmatory evidence. If the father had



had a negative employment x-ray film nine months previously and now is an open case of tuberculosis there is certainly strong presumptive evidence that a positive tuberculin test in his son represents fresh, active tuberculosis regardless of symptoms, x-ray findings, or age.

As early as we can find active tuberculosis we must treat specifically to secure the earliest and best possible healing. During a delay of three or more months untreated primary lesions of any size may undergo considerable caseation in which tubercle bacilli can more effectively barricade themselves. Once the primary infection has been allowed to go untreated, future routine follow-up chest x-ray films are no insurance against tuberculous meningitis, reinfection tuberculosis or a lumbar spine lesion. (One wonders what proportion of the present day geriatric tuberculous patients had onset of tuberculosis in childhood.)

The oldtime standard of a three-month interval between tuberculosis checkups should be discarded during the early observation period of recently exposed children.

The child who has a negative tuberculin test when first checked as a tuberculosis contact is in a potentially dangerous, if not already in an actually dangerous situation. If he is sick he could be anergic from overwhelming tuberculous infection; if he is healthy he may be in the incubation period of his infection.

Above all we don't want to give the parents of these apparently healthy, heavy contact, negative tuberculin babies a false sense of security during such a potentially dangerous time as the first three months after he is removed from heavy exposure. Within these three months the baby may become tuberculin positive, develop a generalized spread and marked symptoms. If at the first contact checkup at the tuberculosis clinic there is proper orientation of the mother on the daily recording of the child's temperature and all his symptoms and bringing him every few weeks for scheduled clinic appointment for observation and repetition of the (negative) tuberculin test for at least two months, we should be able to practically prevent this type of baby being treated unsuccessfully for bronchopneumonia and then worked up from a tuberculosis standpoint elsewhere and finally referred back to the tuberculosis clinic or admitted to the sanatorium.

Admission to the sanatorium makes it easier to complete the investigation and to start the child on his drug and rest schedules. It gives the parents a better insight into the course of treatment in store for the child and also it gives the illness-wrecked home a chance to get organized for the job of cooperating with the clinic in caring for the child after he is discharged from the sanatorium. A child whose lesions are stabilizing under well-tolerated drug therapy is better off in a good reliable home where life is more normal and it is easier to prevent intercurrent infections and contagious diseases. However, it is lack of reliability on the home front which leads to abuse of drug therapy and is the problem most likely to be insurmountable in the early adequate treatment program.

There will always be some children who will need to take all of their

treatment course in the sanatorium since releasing them to the home would be tantamount to discontinuing treatment.

With a program of early specific therapy fewer patient sanatorium days will be required, but in order to reach this goal there will be required (1) a lot of capable cooperation from the child's family, and (2) an increase in clinic and field personnel. There must be dependable people who will keep check on how the treatment program in the home is being carried out, on the failure to keep clinic appointments and many other factors associated with completing the treatment of a tuberculous child in the home. We probably should enlist, train, and supervise a militia of mothers and grandmothers rather than increase the standing army of nurses and medical attendants in the sanatorium. In this way the little patients will move through the limited number of sanatorium beds at a rate which will permit the necessary therapy being given to all these children at the most advantageous time.

The following cases will illustrate and somewhat summarize what has been said above.

*Case 1:* Denise, a Negro girl, lived in the same home with her aunt in April and May of 1952 but when this aunt was hospitalized for tuberculosis two months later, the child was not checked as a "contact" case but showed up as a pilot case a year later—almost a year too late. Her mother did not notice symptoms until about May 15, 1953 when she developed a cold which became more severe and was thought to be pneumonia. On June 17, 1953, she was seen in a non-tuberculosis clinic and on June 18, in a second clinic where patch test and x-ray film were found to be positive and she was admitted to Maybury Sanatorium on June 19, 1953 as a semi-emergency. She was four years old, acutely ill, listless, 25 per cent underweight and had a troublesome, brassy, productive cough. The sputum was positive for tuberculin bacilli on both smear and culture. Her x-ray film showed extensive lymph node enlargement

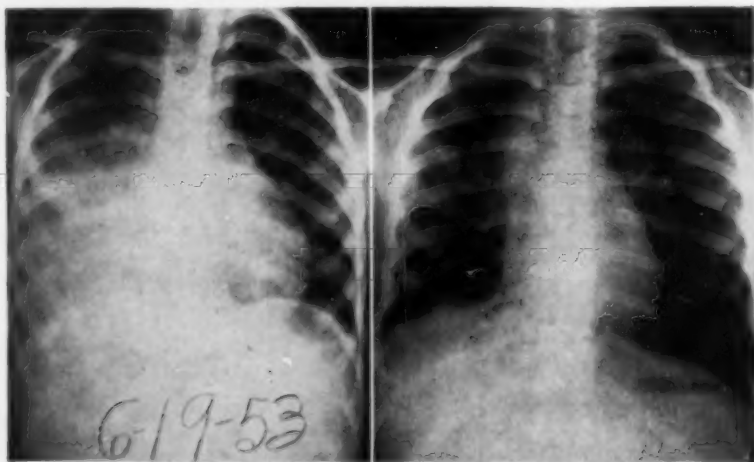


FIGURE 4A

FIGURE 4B

*Figure 4A* (Case 1): Admission on June 19, 1953. Dense infiltrations in lower  $\frac{3}{4}$  right lung with 2 cm. cavity and extensive lymph node enlargement at and above the right hilum.—*Figure 4B*: Taken on June 21, 1955 showing the clearing after 2 years of antimicrobial therapy. There is atelectasis of right lower and middle lobes with extensive saccular bronchiectasis.

at and above the right root and a large complicated primary lesion with a 2 cm. cavity in the lower two thirds of the right lung. After two years of INH plus SM and/or PAS therapy there was marked clearing. At this time a bronchogram demonstrated marked contraction of the middle and lower lobes into a small space near the heart. There was extensive saccular bronchiectasis in both these collapsed lobes which were surgically removed. The surgical specimen showed not only the atelectasis, fibrosis, and bronchiectasis but also partially calcified caseous tissue containing tubercle bacilli. (These failed to grow out in nine months of culturing.) The operation was long and tedious due to fibrosis extending into and around the root of the lung. Calcifying mediastinal lymph nodes remained. Her postoperative course was uneventful and after a total of 32 months in the sanatorium she was allowed to go home to continue INH-PAS in the Chemotherapy Clinic for an additional year.

*Case 2:* Richard, a white boy, was 17 months old when his mother was hospitalized with advanced tuberculosis and a history of cough for six months. The mother absconded twice and at no time was Richard checked as a contact. He seemed to do well until about five years old when he began to chill and tire easily. Four months later (a month before admission to Maybury) he had occasionally frontal headaches and his right eye seemed to turn inward. A week or so later he awoke one morning with right-sided paresis and convulsive movements. He had difficulty walking, slurred speech, urinary incontinence, drooling, and intermittent fever. Three weeks later the jerking movements were more severe, he was choking on his saliva and was having trouble hearing. He was finally taken to a non-tuberculosis hospital where an intracranial tumor was diagnosed. A positive Mantoux test, and hilar calcifications were found. Spinal fluid was normal. SM-INH-PAS were started on the presumptive diagnosis of tuberculoma of the brain. Therapy has been continued since his admission to Maybury on July 28, 1955, and he has responded well except for some residual paralysis of face, left hand, and both feet. He is able to get about in a walker. Therapy is being continued.

*Case 3:* Larry, a Negro boy, had BCG at four days of age in September, 1955, the same month in which his father's pre-employment x-ray film showed pulmonary tuberculosis. The father was admitted to the sanatorium when Larry was six weeks old but absconded after one month and was not rehospitalized until Larry was seven months old.

At one month of age, Larry had first contact checkup in the tuberculosis clinic. Tuberculin test was negative. At two months of age he was seen in a non-tuberculosis clinic because of fever and irritability and was treated for pharyngitis. On the second non-tuberculosis clinic visit he had cough and frequent loose stools. On the third visit there, after a month of symptoms, tuberculin test was four plus and x-ray film



FIGURE 5 (Case 3): X-ray film of right elbow showing destructive process in ulna with posterior dislocation and gross soft tissue swelling.

strongly suggestive of tuberculosis. He was referred to the tuberculosis clinic where the diagnosis of active primary tuberculosis was made. In the next three weeks he was seen three times in the non-tuberculosis clinic with coughing, sweating, rhonchi, wheezes, and fever to 104.4°. He was again referred to the tuberculosis clinic but did not go there until more than two months later. Shortly afterward he again began to have a high fever, this time accompanied by a hot, painful, swollen elbow and after a week of these symptoms was seen in a different non-tuberculosis clinic. Tuberculin test was again positive. X-ray film showed hilar adenopathy and "probable tuberculosis of the elbow." The elbow was surgically drained and cultures were subsequently reported positive for tubercle bacilli. He was started on INH and SM and after two months he was transferred to Maybury Sanatorium on June 8, 1956, when nine months of age. He was overweight, afebrile, and had a swollen elbow with draining sinus.

On x-ray film the right elbow showed posterior dislocation of the ulna and considerable destruction of the articulating surface of the ulna and extensive soft tissue swelling. The chest x-ray film showed questionable lymph node enlargement and parenchymal lesion on the right side. Isoniazid-streptomycin were continued and PAS added. Four months later SM was discontinued. A month after admission the sinus had closed. At present he has a completely functional and normal appearing elbow.

*Case 4:* Paul, a two year old white boy, was admitted to Maybury April 22, 1957, with history of exposure dating back four to eight months. After his grandfather, in whose home he visited frequently, was hospitalized with advanced tuberculosis March 11, 1957, Paul had his first contact checkup. Mantoux was found to be positive. About February 13, 1957, he became irritable, had anorexia, marked weight loss, and sore throat. He was treated in two different doctors' offices and then admitted to a non-tuberculosis hospital because of continuing symptoms, fever of 104° F. and vomiting. In the hospital it was necessary to have tube feeding. His symptoms had been considered due to nervousness because his mother had gone back to work. His x-ray film showed a well developed, fine (fatal-type) of miliary tuberculosis. He was started on INH-SM-PAS and transferred to Maybury Sanatorium where on continued drug and supportive treatment he is showing good improvement.

*Case 5:* Kenneth's first contact checkup was 12 days before his mother's rehospitalization. He was still in the incubation period and, therefore, tuberculin test and x-ray film were negative. This gave a false sense of security and he was scheduled for routine checkup in three months. Two weeks after this x-ray film inspection and a few days after his mother was hospitalized he began to lose weight, have frequent colds, and be irritable. This was thought to be due to lonesomeness for his mother. After two weeks of symptoms he was seen in a non-tuberculosis clinic for the first time and only this extreme irritableness was found then and at the second clinic visit three days later. On the third and fourth non-tuberculosis clinic visits, temperature was 101° F. and he was treated for ear and throat infections. Six weeks later he was listless, feverish, coughing and vomiting and having difficulty walking. After 10 days of treatment in the doctor's office he was referred back to the non-tuberculosis clinic for hospitalization but when x-ray film showed evidence of advanced miliary tuberculosis

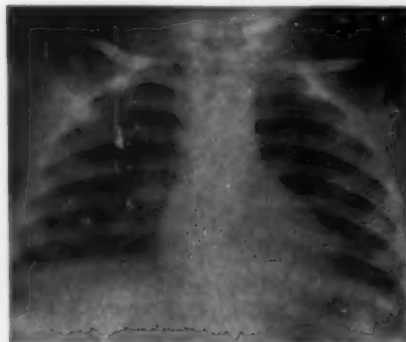


FIGURE 6A



FIGURE 6B

*Figure 6A* (Case 5): Opened on January 10, 1955. Contact checkup film was normal.—  
*Figure 6B:* Admission film taken July 19, 1955 shows extensive miliary tuberculosis.

he was admitted to Maybury as an emergency. The tuberculin test was positive and cultures of swallowed sputum were positive for tubercle bacilli. Spinal fluid was normal.

He had fever, shortness of breath, dusky pallor, constant distressing cough, and marked fatigue. He was placed in the oxygen tent and given isoniazid and streptomycin in high dosage and PAS in routine dosage and is making a good recovery.

#### SUMMARY

Every effort must be made to advance the diagnosis and management of early tuberculosis in children. The proper use of the tuberculin test will help do this. A positive tuberculin test is specific and is diagnostic of active tuberculosis in a child if he is very young, if it is preceded by a recent negative test, if it is associated with known contact with an "open" case of tuberculosis or if it is supported by clinical, x-ray film or laboratory findings.

The value of x-ray film in diagnosing early tuberculosis in children is definitely limited because it is difficult to obtain a good roentgenogram, the lesions may be obscured by intrathoracic structures, the shadows may be mistaken for other types of disease and because there is nothing specific about early primary tuberculosis lesions, the lesions may not have developed to the extent that they can be demonstrated by x-ray film.

Case history is extremely important including dates—dates of contact, of onset of symptoms, of negative and positive tuberculin tests and of negative and positive x-ray film findings. Among 335 children treated in Maybury Sanatorium since January 1, 1956, the age of onset was under five years in more than 75 per cent. These home infected children should serve as "pilots" in searching for "open" cases of tuberculosis. The source of contact was found among members of the family in 35 per cent and among other close relatives in 34 per cent of the cases. In 15 per cent the contact was an uncooperative tuberculous patient.

Symptoms are variable but not specific. Nearly 95 per cent of the 335 children had symptoms. Cases diagnosed in non-tuberculosis hospitals and clinics were more likely to have severe symptoms than those diagnosed in the tuberculosis clinic. Many children known to be exposed and/or infected were treated for various other conditions before the real cause of illness was suspected. During these periods of time some of these children progressed to serious tuberculosis—five such cases are presented. A plea is given to discard the routine three-month interval between checkup examinations in the management of early tuberculosis in children. Serious progression often occurs within three months.

Antimicrobial therapy must be used at the earliest possible time in tuberculosis in children—i. e., when the tuberculin converts or if the child has had heavy exposure and is sick (anergic). The younger or the sicker the child the more urgent is treatment. We use Isoniazid 7-6 mg./Kg./day with PAS 150-100 mg./Kg./day. It is tolerated well and no harm will result from its use in suspected cases but if not used and the child develops serious tuberculosis there is no way to recover the early advantageous point which was missed.

We urge that more attention be given to tuberculosis in young children. We advocate the tuberculin testing of all pre-school children in clinics and



doctors' offices and the proper handling of all positive reactors. We recommend early treatment of all cases, in the hospital preferably for the initial part and in the properly organized home for the completion.

#### RESUMEN

Debe hacerse toda clase de esfuerzos para adelantar el diagnóstico y el tratamiento de la tuberculosis primaria en los niños. El adecuado uso de la tuberculina ayudará para esto. Una reacción positiva de tuberculina es específica y diagnóstica de tuberculosis activa en un niño si es muy joven, si además es precedida de una reacción negativa reciente, si se sabe que está en contacto con un caso "abierto" de tuberculosis o bien si esto se apoya en la investigación clínica, radiológica o de laboratorio.

El valor de los rayos X para diagnosticar la tuberculosis primaria en los niños, es francamente limitado por la dificultad de obtener buenas radiografías; las lesiones por otra parte pueden ser ocultas por las estructuras intratorácicas; las sombras pueden ser tomadas equivocadamente por otra enfermedad y como no hay nada específico referente a las lesiones de tuberculosis primaria, éstas pueden no haberse desarrollado hasta el grado de poderse demostrar en la película de rayos X.

La historia clínica es muy importante incluyendo fechas de contacto, de principio de síntomas, de pruebas negativas y positivas de tuberculina, y de los hallazgos positivos a los rayos X.

Entre 335 niños tratados en el Sanatorio Maybury desde Enero de 1956, la edad del principio fué bajo los cinco años en más de 75 por ciento de los casos. Estos niños infectados en sus casas deben servir como "pilotos" para buscar los casos abiertos. La fuente de contacto fué encontrada entre los miembros de la familia en 35 por ciento de los casos y entre otros parientes próximos en 34 por ciento. En 15 por ciento el contacto era un enfermo no deseoso de cooperar para la protección.

Los síntomas son variables pero no específicos. Aproximadamente 95 por ciento de 335 niños tenían síntomas. Los casos diagnosticados en hospitales que no son para tuberculosos y en las clínicas posiblemente presentan más frecuentemente síntomas más severos que los diagnosticados en las clínicas de tuberculosos. Muchos niños conocidos como expuestos y/o infectados se trataron por otras causas antes de que la causa real de su enfermedad se sospechase. Durante estos períodos de tiempo algunos de los niños marcharon hacia tuberculosis grave. Cinco de tales casos se presentan. Se reclama que se descarte el intervalo de rutina, de tres meses entre los exámenes en el control de la tuberculosis primaria. Serios avances de la enfermedad a veces ocurren durante tres meses.

La terapéutica antimicrobiana debe usarse tan tempranamente como sea posible en la tuberculosis infantil ya sea cuando la tuberculina vira o aún antes si el niño está altamente expuesto.

Mientras más joven o más enfermo parezca el niño, más importante es el tratamiento. Nosotros usamos isoniácida 7-6 miligramos por kilo por día asociando PAS 150-100 mgrms. por kilo por día.



Esto es bien tolerado y ningún daño resulta de su uso, pero si se nota que el niño presenta tuberculosis grave no hay manera de recuperar las ventajas que al principio se han perdido.

Urgimos que se ponga más atención en la tuberculosis entre los niños muy pequeños. Aconsejamos la prueba tuberculínica en todos los niños pre-escolares en las clínicas y en los consultorios de los médicos, así como aconsejamos el trato adecuado de todos los reactores positivos. Recomendamos tratamiento temprano en todos los casos en el hospital de preferencia para la iniciación y el hogar bien organizado para la continuación.

#### ZUSAMMENFASSUNG

Es muss alle Anstrengung unternommen werden, um die Diagnose und die Behandlung der kindlichen Früh-Tuberkulose zu fördern. Die entsprechende Anwendung des Tuberkulintestes wird dazu beitragen. Ein positiver Tuberkulintest ist spezifisch und ist gleichbedeutend mit der Diagnose einer aktiven Tuberkulose bei einem Kind, wenn es sehr jung ist, wenn in diesem Fall kürzlich erst eine negative Probe vorausgegangen ist, wenn er gleichzeitig auftritt mit einem bekannten Kontakt mit einem "offenen" Fall von Tuberkulose, oder wenn er unterstützt wird durch Klinische, röntgenologische oder Laboratoriums befunde.

Der Wert von Röntgenaufnahmen bei der Diagnose einer frühen Kinder-Tuberkulose ist fest begrenzt, da es schwierig ist, eine gute Röntgenaufnahme zu erhalten, ferner die Herde verdeckt sein können durch intrathorakale Körperteile, weiter die Schatten irrtümlich für eine andere Krankheitsart gehalten werden können und schliesslich—weil nichts besonders kennzeichnend ist für frühe tuberkulöse Primärherde—die Herde sich vielleicht noch nicht so weit entwickelt haben, dass sie sich durch eine Röntgenaufnahme nachweisbar lassen.

Die Vorgeschichte ist von ausserordentlicher Wichtigkeit, inbegriffen die Zeitangaben—Zeitangaben über Kontakt, Beginn der Symptome, des negativen und des positiven Tuberkulintestes und von negativen und positiven Röntgenaufnahmenbefunden. Unter 335 im Maybury-Sanatorium seit 1.1.1956 behandelten Kindern betrug das Alter zu Beginn der Erkrankung in mehr als 75% weniger als 5 Jahre. Diese in ihrer Häuslichkeit infizierten Kinder müssen als "Lotsen" dienen auf der Suche nach "offenen" Fällen von Tuberkulose. Die Infektionsquelle fand sich unter Familienangehörigen in 35% und unter anderen näher Verwandten in 34% der Fälle. In 15% war die Quelle ein asozialer tuberkulöser Patient.

Die Symptome sind variabel, aber nicht spezifisch. Etwa 95% der 335 Kinder hatten Symptome. Bei Fällen, die in nicht tuberkulösen Hospitälern und Ambulanzen festgestellt waren, war es wahrscheinlicher, dass schwere Symptome bestanden, als bei solchen, die in Tuberkulose-Anstalten diagnostiziert wurden. Viele Kinder, von denen bekannt war, dass sie exponiert waren und die oder die infiziert worden waren, wurden auf verschiedenste andere Krankheiten behandelt, ehe man die wahre Krankheitsursache vermutete. Während dieser Zeitabschnitte entwickelte sich bei einigen dieser Kinder Eine Schwere Tuberkulose. Über 5 solcher Fälle

wird berichtet. Es wird dafür eingetreten, sich frei zumachen von den routine-mässigen 3-monatigen Intervallen zwischen der genauen ärztlichen Durchuntersuchung bei der Betreuung der frühen Tuberkulose bei Kindern. Es kommt oft zu bedenkliche Progredienz innerhalb von 3 Monaten.

Antimikrobielle Therapie muss angewandt werden zum frühest möglichen Zeitpunkt bei der Kindertuberkulose-, d-h- wenn die Tuberkulinprobe von Negativ zu Positiv umschlägt oder sogar noch vor diesem Zeitpunkt, sofern das Kind stark exponiert gewesen war. Je jünger oder je mehr schwer krank das Kind ist, desto wichtiger ist die Behandlung. Wir gebrauchen INH 7-6mmg-kg-tägl. mit PAS 150-100mmg-kg-tägl. Dies wird gut vertragen und dieser Modus hat keinen Schaden zur Folge bei verdächtigen Fällen; wird davon aber kein Gebrauch gemacht, und bei dem Kind entwickelt sich eine schwere Tuberkulose, gibt es keine Möglichkeit, die frühen vorteilhaften Stufen wieder-zugewinnen, die verpasst wurden.

Wir betonen nachdrücklich dass der Tuberkulose bei Kleinkindern mehr Aufmerksamkeit gewidmet werden muss. Wir befürworten die Tuberkulinprüfung aller Kinder im Vorschulalter in Ambulanzen und ärztlichen Sprech-Stunden und die geeignete Handhabung aller Fälle mit positiver Reaktion. Wir empfehlen die Frühbehandlung aller Fälle und zwar stationär vorzugsweise für die Einleitung der Behandlung und in entsprechend organisierter Häuslichkeit für den Abschluss.

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# The Struggle for Eradication of Tuberculosis

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Advances in drug therapy have required changes in public health procedures without discarding the time tested practices of tuberculosis control. Chemotherapy and modern advances in thoracic surgery have resulted in a sharp drop in mortality, declining morbidity, shorter duration of treatment and diminished hospital confinement. No known single or combination of drugs destroys all tubercle bacilli in the body and the outlook for improved therapy must depend upon research laboratories. Our present anti-tuberculosis drug therapy fails in some cases and has no effect on those infected with drug resistant bacilli. Among others with widespread bilateral disease, especially the elderly, active disease cannot be arrested and such persons must be isolated.

Prior to the advent of streptomycin, therapy depended largely on bed rest, nutrition and collapse procedures. Treatment was largely in the hands of specialists in pulmonary disease and only a small percentage of patients was under the care of general practitioners. The average physician could not spare the time necessary on a single patient for proper coverage of medical advice and treatment after making a diagnosis of active disease. The case was referred to a sanatorium or to the phthisiologist. Modern drugs have simplified therapy, and physicians who never treated tuberculosis under the old regime, are now taking care of many ambulatory patients. The doctor now specializing only in tuberculosis is a rarity. A result has been that more patients are refusing hospitalization because they or their physician rejects institutional care. Our problem, now is not only with the "good chronic," with lingering tuberculosis and positive sputum, who is allowed to go about his occupation, meantime spreading the disease, but also with early, and moderately advanced cases under therapy who form an added source of infection. Patients without hospital supervision have been arrested, but more have progressed to advanced stages before being sent to institutions. Widespread practice of ambulatory chemotherapy has resulted in development of drug resistant organisms in a number of cases. The unhospitalized tuberculosis patient is a major health problem, as a source of infection.

## *Mortality*

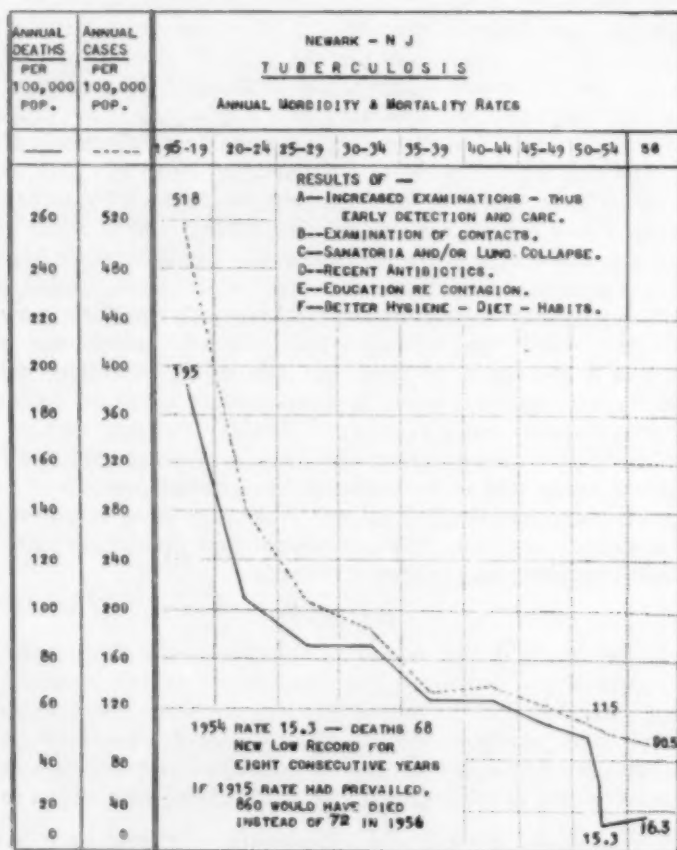
Records for the past half century show the steady drop in mortality rate. In spite of the declining rate, tuberculosis is still responsible for more deaths than all other infectious diseases combined. Once a disease of young adults, the problem now concerns the aged, especially old men. Prior to the advent of anti-tuberculosis drugs, bed rest and collapse therapy helped the rate to fall. Subsequent to that time, campaigns to locate

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the disease before it was too widespread, and improved medical and surgical treatment resulted in a sharp decline of fatality rate. The first eight years following the use of streptomycin and later other anti-tuberculosis drugs, demonstrated our most rapid decrease of mortality in history. The sharp drop slowed in 1954 when a plateau was reached in curbing tuberculosis deaths. In 1955 the same death rate occurred as the previous year, and in 1956 there was a rise. The drugs have not been controlling the disease in all cases and in some instances, the bacilli have been reactivated. Some individuals kept alive by modern therapy and apparently arrested, have reactivated and died.

### Morbidity

The morbidity rate has been declining for several years but not as rapidly as the death rate. The drop in the annual incidence of tuberculosis would suggest that the number of cases infected is declining. This may lead to an impression with the falling death rate that tuberculosis is becoming a minor problem. In dealing with a disease characterized by



chronicity and relapses, an arrested case can flare into activity. Some individuals probably harbor the tubercle bacilli since childhood, while others contract it in adult life. The apparently arrested and inactive case can still harbor live tubercle bacilli which can be reactivated. The arrested case with stationary x-ray findings may still have small necrotic lesions that can flare into progressive tuberculosis. The most lucrative source of case finding is still the family contacts of an active or suspicious case. Epidemiological investigation of family contacts results in discovery of more new infections that perpetuate tuberculosis than any other method. The decreasing morbidity rate does not confirm estimates of the Public Health Service of 400,000 active cases of tuberculosis in the United States and twice that number of inactive cases.

Newark, New Jersey, is an industrial city with a population estimated at 443,000 (360,000 whites, 83,000 negroes). Tuberculosis control program is based on:

1. Mass x-ray film surveys throughout the city with spot checkups in areas where the tuberculosis incidence is high.
2. Tuberculin testing of children with x-ray film and follow-up, not only of the positive reactors but of members of the families and other contacts.
3. Isolation of the open active cases.
4. Improved medical and surgical procedures of therapy.
5. Close supervision of all contacts.
6. Commitment of cases that refuse to co-operate and form a public health menace.

The unknown case is responsible for a substantial amount of infection. This source is far more dangerous than our known cases. Some patients have been diagnosed but never reported to the public health authorities. A few undiagnosed and untreated cases can start a new epidemic of tuberculosis. Regardless of all case finding methods, many are never located. They have neither been recognized nor diagnosed until just before or after death. Since the advent of chemotherapy, this great hazard has been increasing. The following chart illustrates the percentage of unknown cases in Newark, N. J., reported after death.

	Per Cent		Per Cent
1944	24	1951	21
1945	20	1952	22
1946	24	1953	29
1947	22	1954	22
1948	21	1955	30
1949	23	1956	39
1950	37		

#### *X-ray Film Surveys*

When subjective complaints are absent and there is no clinical finding, the x-ray film is the most powerful instrument in locating minimal lesions. An early diagnosis helps not only in locating the source of infection but

gives an excellent chance for complete recovery. X-ray film surveys have been conducted annually for a number of years on a voluntary basis. The essence of the survey is to locate the active or suspicious case. Most individuals will have had no contact with an infectious case, but cases without known contact can be located. Success of the survey with mobile and stationary units largely depends upon the preliminary educational program. Preceding a campaign, in an effort to reach a large segment of the population, the local press, radio, addresses before social and fraternal groups, motion pictures, placards in buses, and a sound truck are utilized. The drives are intensified in "high incidence or target areas" where statistics demonstrate most active cases reside. A major problem is to attract to the units, individuals most likely to harbor tubercle bacilli. The derelict, the chronic alcoholic and floater found in slum areas and in poor housing districts usually avoid survey. Some individuals knowing or suspecting that they have tuberculosis do not respond as they do not want to be known to health authorities. The screening forms only an initial step. Without an intensive follow-up, the entire program is a waste of public funds.

The value of a survey can be estimated in: 1. Stimulating public interest in tuberculosis. 2. Locating cases that have been arrested for many years that have reactivated. 3. Finding inactive cases and following up new contacts. 4. Discovering other pulmonary abnormalities (pneumonia, pneumoconiosis, fungus infections, malignancy etc.) 5. Noting cardiac enlargements and reporting these to the family physicians.

Surveys include only a small percentage of the population, leaving the majority without examination for spreaders of the disease. A negative chest film is no assurance that active, progressive disease may not take place in the future.

Present case finding methods are far from satisfactory and repeated surveys have resulted in locating only a small percentage of active cases that were not previously known.

#### *Tuberculin Test*

The tuberculin test, an economic method of case finding, is the best diagnostic tool for determining the absence or presence of infection. A positive reaction indicates that tubercle bacilli have been present and may still be viable. The positive reaction in infants is usually the only evidence of tuberculosis infection, and suggests a close contact with an

ACTIVE CASES OF PULMONARY TUBERCULOSIS LOCATED  
IN MASS X-RAY SURVEYS

Year	X-Ray Films Taken	Active Cases (Not known to Health Dept.)
1953	39,002	17
1954	8,811	8
1955	7,295	7
1956	32,728	11 (80 per cent complete)



active case. Among those who react to tuberculin only a small percentage develop active disease and a long time may elapse between the reaction and the inception of clinical disease. Tuberculin surveys are essential in any public health program. Reactors are potentially active cases and must be followed with x-ray films well into adult life. Tuberculin testing in clinics and in public and parochial schools has been a regular procedure for many years. Not only are the reactors closely followed but also all members of the family and contacts. As the rate of infection decreases, the test is assuming a more prominent place in case finding. The test is important in finding unknown cases of tuberculosis, in diagnosis, and at times, furnishes information as to when infection took place. In routinely testing children, especially when there has been contact with an active case, the time of infection can be estimated when a persistently negative reactor changes to positive. In testing various groups of the population, an index can also be obtained as to which group requires more attention from an epidemiological standpoint. Every reactor should be treated as many will not require medical aid. However, recent convertors should be placed under chemotherapy.

There has been a remarkable decline in the number of reactors during the past 20 years. In the clinic of the Newark Division of Health (where a large portion have been exposed to tuberculosis at home, or where a relative or friend is ill with tuberculosis or where a member of the family died of the disease) the rate is higher among the school children.

In 1935 a survey of 997 children tested produced the following results:

	Number	Negative	Positive
White Children	657	478 — 61 per cent	281 — 39 per cent
Negro Children	229	132 — 44 per cent	167 — 56 per cent

The drop in reactors after 20 years is indicative of the lower proportion of infected children.

1955	1400	163 — 11.6 per cent
1956	1574	186 — 11.8 per cent

Most children tested at the Division of Health are also tuberculin tested at their schools. The majority of the pupils, however, are not known contacts. The following results were obtained:

PAROCHIAL SCHOOLS  
(Children tested in all grades)

Year	Number	Positive	Per Cent
1955	3476	224	6.1
1956	4722	220	4.7

PUBLIC SCHOOLS

Tuberculin testing is routine in Grades 9, 10 and 12, except where known contacts are tested in any grade.

Year	Number	Positive	Per Cent
1955	10,372	534	5.2
1956	14,613	1079	7.3

Follow-up of reactors by x-ray films in 1956 resulted in locating 12 active cases of tuberculosis (that were excluded from school) and 58 ar-

rested. Of the active cases: four were in the Kindergarten to sixth grade, one was in the seventh grade, two in the ninth grade and five in the tenth to twelfth grades.

Incidence of tuberculosis in children can be considered as a yardstick of prevalence of tuberculosis in a community. Evaluation of mortality statistics demonstrates the decline in children under 15 years of age when compared over a period of 20 years.

#### TUBERCULOSIS DEATHS AMONG NEWARK CHILDREN

	White	Negro		White	Negro
1931	7	21	1951	2	3
1932	9	13	1952	2	4
1933	17	16	1953	2	6
1934	7	10	1954	....	2
1935	8	14	1955	....	2
1936	1	16	1956	1	3

#### *Eradication*

Tuberculosis is far from being controlled in spite of education, research and modern medical and surgical therapy. Mass x-ray film surveys will not lead to eradication but may help to diminish the incidence. The tuberculin test should be widely used not only in children but in controlled groups of adults. (School teachers, municipal employees, domestics, food handlers) to locate positive reactors, who must be closely supervised. Every open active case must be isolated and treated and all contacts closely followed up by routine x-ray films. Proper isolation of the known patient will prevent the infection from spreading and thus limit the "pool of communicable disease." The major problem consists of the surviving tuberculous individual with unhealed disease who flares into activity. Eradication must depend upon the absence of infection and early diagnosis with rapid treatment to prevent further spread.

#### SUMMARY

1. Modern chemotherapy has simplified treatment in pulmonary tuberculosis and many active cases are now in the hands of general practitioners.
2. Mortality rates which have been steadily falling, appear to have reached a plateau.
3. Morbidity rates continue to drop leaving the false impression that tuberculosis is diminishing.
4. The unknown and undetected case forms the greatest hazard in a control program.
5. Mass x-ray film surveys only reach a small portion of the population and help to locate a small percentage of active cases.
6. Tuberculin testing and follow-up of the reactors forms the most lucrative method of case finding in a public health program.
7. The number of reactors in children is rapidly declining.

8. Eradication of tuberculosis can only be obtained by reducing the incidence of infection.

#### RESUMEN

1. La quimioterapia moderna ha simplificado el tratamiento de la tuberculosis pulmonar y muchos casos activos están ahora en las manos de los médicos generales.

2. Las cifras de mortalidad que habían estado cayendo constantemente parece que han llegado a una meseta.

3. Las proporciones de la morbilidad continúan cayendo dejando la impresión falsa de que tuberculosis está disminuyendo.

4. Los casos desconocidos y no descubiertos forman el mayor peligro en el problema del control.

5. La investigación por la roentgenfotografía de las masas alcanza sólo una pequeña parte de la población y ayuda a localizar un pequeño porcentaje de casos activos.

6. La reacción tuberculínica y el seguimiento de los reactores forma el método más fructífero de hallazgos en los planes de salubridad pública.

7. El número de reactores entre los niños está declinado rápidamente.

8. La erradicación de la tuberculosis puede sólo obtenerse reduciendo la incidencia de la infección.

#### ZUSAMMENFASSUNG

1. Die moderne Chemo-Therapie hat die Behandlung der Lungentuberkulose vereinfacht und viele Fälle mit aktiven Befunden finden sich jetzt in den Händen von Allgemeinpraktikern.

2. Die ständig abfallenden Sterblichkeitskurven scheinen jetzt ein horizontales Niveau erreicht zu haben.

3. Die noch fortgesetzt abfallenden Morbititätskurven hinterlassen den falschen Eindruck, dass die Tuberkulose zurückgehe.

4. Die unbekannten und die nicht gefundenen Fälle stellen das grösste Problem dar bei der Tuberkulosebekämpfung.

5. Massenschirmbilduntersuchungen erreichen nur einen kleinen Teil der Bevölkerung und tragen dazu bei, einen kleinen Prozentsatz aktiver Fälle zu bestimmen.

6. Tuberkulin-Prüfungen und Nachkontrolle der positiv reagierenden Fälle stellen die am meisten lukrative Methode dar zur Fallsuche in einem Plan der öffentlichen Gesundheitspflege.

7. Die Zahl der positiv reagierenden Kinder geht rapid zurück.

8. Die Ausmerzung Tuberkulose lässt sich nur ermöglichen durch Verringerung der Infektionshäufigkeit.

## Treatment of Pulmonary Tuberculosis with ACTH and Cortisone in Addition to Specific Anti-Tuberculosis Therapy

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In these past years problems of the utmost practical importance have arisen in connection with the use of cortisone and ACTH for patients with pulmonary tuberculosis. Among them the following are outstanding:

1. Does the use of ACTH or cortisone have a deteriorating influence on an active tuberculous process and can it cause a relapse in non-active tuberculous changes?
2. Will a combined treatment, adding antimicrobial drugs to these hormones, prevent unfavorable phenomena as above described?
3. Will the combination of antimicrobial drugs with ACTH/cortisone influence the tuberculous process favorably?
4. And if so, are there indications for the use of steroids in tuberculosis? Which are the suitable doses and what is the average length of time for their use?

The first experiences with ACTH and cortisone in different diseases and especially in rheumatic diseases proved that not only in active but even in arrested tuberculosis the use of these drugs is contraindicated. Many cases have been observed in whom no tuberculosis was found prior to the use of these drugs and in whom severe active tuberculosis appeared after their use. In others a deterioration of inactive processes occurred or new disseminations were found.

Supported by these experiences, the American Trudeau Society warned in 1952 against the use of ACTH and cortisone in tuberculous patients. In their opinion, even a non-active tuberculous process is a danger, potentially, for the patient who is treated with these drugs to combat other diseases. In the past two years these views have undergone considerable change. A number of investigators have shown that ACTH or cortisone in combination with antimicrobial drugs not only are devoid of a negative influence on tuberculosis, but, on the contrary, can help in its cure.

These recent publications have served us as a stimulant to investigate this problem on a number of patients in our hospital. Investigations have been done on 29 patients with pulmonary tuberculosis of whom 14 had active, fresh processes, nine chronic pulmonary tuberculosis with exacerbations and six were chronics without exacerbations; besides one had residual intrapleural effusion following discontinuation of pneumothorax and one residual effusion after extrapleural pneumothorax, two exudative pleurisy with chronic pulmonary tuberculosis, and one chylous peritonitis of tuber-

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culous origin. There were also three with allergic rashes, two of which in the form of nonthrombocytopenic purpura as a complication after treatment with PAS and three with severe vertigo as a complication after treatment with streptomycin. In addition two had inactive pulmonary tuberculosis combined with severe asthma and two had cystic lung disease with asthma.

### Methods

Treatment with ACTH and cortisone was given to patients ranging in age from three to 68 years. Excluded from the treatment were those suffering from hypertension, anamnesis of gastric or duodenal ulcer and diabetes mellitus. Before treatment was started, electrocardiogram, liver function test, blood electrolytes, Thorn test, and 17-ketosteroids in the urine, in addition to the routine examinations, were done. During the period of treatment with steroids the following examinations were made: Eosinophil count once weekly, 17-ketosteroids once in two weeks, electrolytes once in two weeks, electrocardiogram once monthly, x-ray film and tomogram at least once monthly, and screening twice weekly. Weight was controlled once weekly and in addition to all this, blood pressure was taken daily as well as examination of urine for sugar done every day and blood sugar once in two weeks. Children and adults, not older than 40, whose adrenals were regarded as in relatively normal condition, usually received ACTH. Adults over 40 and aged patients received cortisone or meticorten. The majority of cases with severe chronic tuberculosis received either cortisone or meticorten, assuming that the function of their adrenals might be impaired by their long-standing disease. Of course there is no absolute proof for this assumption. The determining factors were the auxiliary examinations. In those cases where the number of eosinophils rose above the level maintained prior to treatment and the amount of 17-ketosteroids in the urine sank, we changed the ACTH for cortisone or meticorten. Two weeks after termination of treatment we examined the function of the adrenals by means of the Thorn test and of eliminations of 17-ketosteroids in the urine. In the great majority of cases these examinations gave normal results. In single cases, where cortisone had been given for a longer period of time after which the above mentioned examinations gave unsatisfactory results, an additional treatment, consisting of 10 mg. ACTH daily for a period of seven to 10 days resulted in bringing back to normal the adrenalin function within one to two months. All except those who received meticorten were on a low-salt diet, with the addition of potassium either in the form of potassium chloride 1-2 Grams daily or in the form of orange juice which contains a sufficient amount of potassium.

The schedule of hormone administration was as follows:

Meticorten		Cortisone		ACTH Gel.	
20	mg. daily for 10 days	100	mg. daily for 7 days	60	mg. daily for 5 days
15	mg. daily for 15 days	75	mg. daily for 7 days	50	mg. daily for 7 days
10	mg. daily for 20 days	50	mg. daily for 40 days	25	mg. daily for 20 days
5	mg. daily for 10 days	25	mg. daily for 5 days	12½	mg. for rest of treatment
2½	mg. daily for 5 days	12½	mg. daily for 3-4 days		

Administration of the hormones was gradually discontinued until the smallest doses were given towards the end of the course. Almost half of the patients received during the first period of investigation the hormones in the course of three months. The other half in the course of two months, in smaller doses. All the patients received antimicrobial treatment at the same time (streptomycin, PAS, INH simultaneously). The first cases were given streptomycin every day and the rest twice weekly. The results were similar.

### Results

Analyzing results, we wish to emphasize on the clinical and radiological changes and the complications that occurred during the hormone therapy (Table I).

1. *Clinical Changes:* Temperature in all cases sank to normal during the first days of treatment and remained so for the rest of treatment as well as after its termination. The general condition of the patients underwent such a speedy and dramatic improvement as has, it is our impression, never been seen during antimicrobial treatment alone. It is worth noting already at this point, that not always has the above mentioned improvement been in accordance with the radiological one. In conjunction with the disappearance of toxic symptoms, an euphoria became apparent and the increase of appetite was such as to lead to immediate gain in weight, an average of more than 5 kilograms during the first month, and that not on account of a hidden edema (fluid imbalance), as weight remained unaltered also after termination of hormone treatment (Table II).

Cough and expectoration diminished rapidly, especially in fresh cases. Two cases of non-active tuberculosis and two with chronic cystic lung diseases, complicated by severe asthma, almost in status asthmaticus showed considerable improvement after two days and the improvement continued for the duration of treatment even with small maintenance doses. Two cases with non-thrombocytopenic purpura, three with an expanded allergic rash, and one of severe Quincke oedema as a result of streptomycin or PAS therapy, were cured in several days and the administration of the

TABLE I  
RESULTS OF TREATMENT

	No. of cases	Good	Fair	No change	Deteriorated
Fresh tb:					
Mod. adv.	6	3	3	—	—
Far adv.	8	5	3	—	—
Total	14	8	6	—	—
Chronic tb:					
Without exacerbation	6	—	2	4	—
With exacerbation	9	1	5	3	—
Total	15	1	7	7	—

Good—i.e.—closure of cavities, disappearance of infiltrations, sputum negative in cultures.

Fair—marked diminution of cavities, marked resorption of infiltrations and sputum negative.



TABLE II  
INCREASE IN WEIGHT

	Up to 5 Kg.	Up to 10 Kg.	More than 10 Kg.
Fresh tb	1	9	4
Chronic tb	8	4	3
Total	9	13	7

hormones for three to four weeks more enabled us to continue the antimicrobial treatment without disturbances.

At this point we wish to report the following outstanding case: this 57 year old woman, developed a severe allergic rash all over the body, distressingly itching, during antimicrobial treatment. After discontinuation of antibiotics she was given antihistaminic drugs; the rash diminished considerably, but returned in an even more severe form after streptomycin was re-added to the drugs in use. At this point we started on cortisone and before the rash disappeared, streptomycin was again administered, even in daily doses. In spite of this the rash disappeared completely; she continued to receive antibiotics in use in combination with cortisone for another three weeks without side effects, and no side effects were noted even after cortisone was discontinued, while the antibiotics were continued. Similarly good results were achieved in two patients with vertigo after streptomycin administration. In two cases, one with effusion after extra-pleural pneumothorax and one in whom intra-pleural pneumothorax was abandoned, and effusion kept returning after thoraco-centeses and antibiotic treatment, cortisone was started. On two occasions one week apart thoraco-centeses were performed and each time 1 cc. of hydrocorton (25 mg.) were injected into the pleural and extra-pleural spaces respectively. At the same time the patients were given cortisone per mouth, covered by all three antibiotics. The effusion disappeared completely, without relapse. In one case of acute exudative pleurisy with high fever and bad general condition, three liters of serous liquid were aspirated, 1 cc. of hydrocorton was injected and cortisone given per mouth. After one week another 300 cc. of fluid was aspirated and again hydrocorton was injected. The liquid disappeared completely after three weeks and the patient remained with antibiotic treatment only (Figures 1 and 2). It is worth mentioning, that after the first injection of hydrocorton the patient felt great relief, stopped perspiring, the fever decreased to normal within two days, the appetite increased and body weight increased three Kg. weight during the first two weeks. The same course could be observed in the second of the two cases. The effusion disappeared after six days.

In the case of a young Arab girl, tuberculous peritonitis with ascites was diagnosed. Laparotomy was performed in another hospital. For a number of months she was given antimicrobial treatment without effect and aspirations of the fluid had to be done several times on account of reappearance of effusion. She was transferred to our hospital for continuation of treatment where chylous peritonitis was found, apparently due to rupture of a lymph vessel on a tuberculous basis. After one month's

treatment with cortisone combined with antibiotics the effusion disappeared completely, and after a few months she was sufficiently recovered to be discharged in good condition.

Two patients, having suffered for years from chronic cavernous pulmonary tuberculosis, had been bedridden for the past few months on

FIGURE  
1

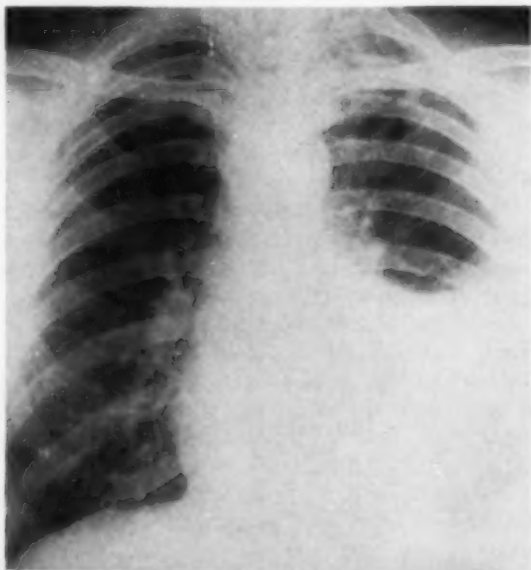
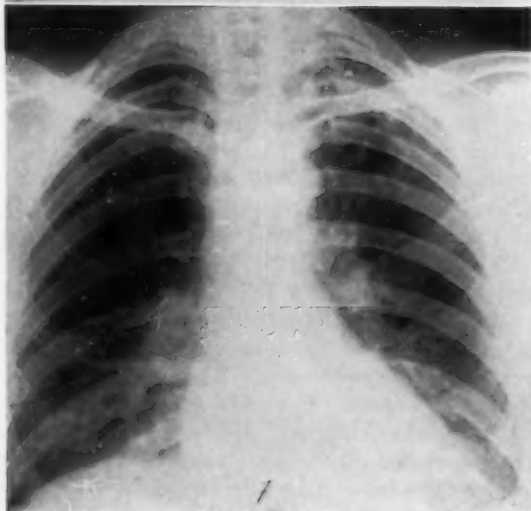


FIGURE  
2



*Figure 1:* T. L., 44 years old, male, left tuberculous exudative pleurisy with old fibrotic changes in the left apex. July 1, 1956, Temp. 38.6 (Celsius). *Figure 2:* July 24, 1956. Complete re-expansion of the left lung. Sinus free. Free movements of the left diaphragm.

TABLE III  
BACTERIOLOGICAL RESULTS

	B.K. Positive	B.K. Negative
Fresh tb:		
Before	12	2
After	3	11
Chronic tb:		
Before	13	2
After	9	6

account of respiratory insufficiency and complete cachexia. In the course of three to four months they were given cortisone, beginning with a daily dose of 100 mg. which was gradually diminished. Their general condition improved greatly, they gained weight, one of them up to 14 Kg. They could walk without breathing difficulties, their general outlook grew more confident; in spite of the fact that radiologically no improvement could be ascertained.

Bacteriologically a sputum conversion of 75 per cent was found in fresh cases after two to three months of treatment which surpasses the percentage that has been achieved after treatment of equal length with antibiotics only (Table III). It is worth noting here that not one of the patients who was negative when treatment was started, converted to positive, neither during nor after termination of treatment.

2. *Radiological Changes:* (Table IV). In patients with pulmonary tuberculosis disappearance or considerable absorption of the exudative changes could be observed following combined treatment with cortisone and antibiotics after shorter periods of time than in patients who received antibiotics only. The most striking absorption was seen in bronchopneumonic or miliaric forms. Interesting to observe was the influence of the

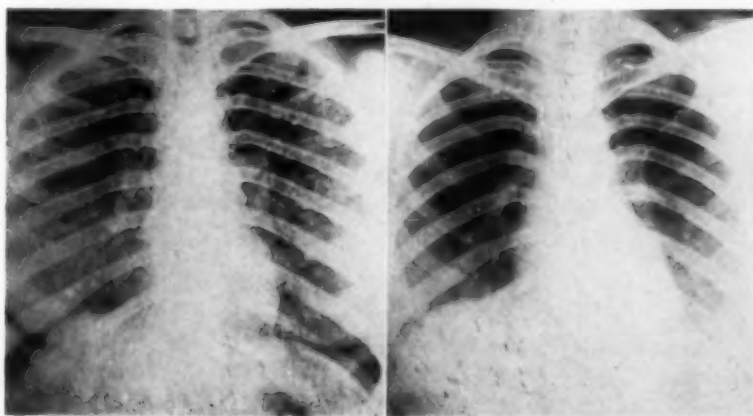


FIGURE 3

FIGURE 4

Figure 3: Ch. S., 30 years old, female, October 10, 1955, bilateral disseminated tuberculosis. Positive for B.K., Temp. 38.7 (Celsius). Figure 4: Ch. S., January 23, 1956, after three months of cortisone treatment: Disappearance of all tuberculous exudative changes. Small fibrotic changes in the left apex.

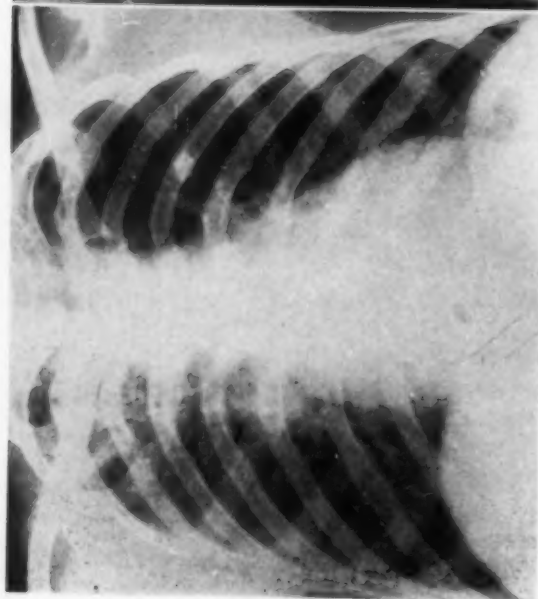


FIGURE 5

Figure 5: M. C., 13 years old, male. October 20, 1955. Right side pulmonary tuberculosis. Infiltrations with cavitations in the right upper lobe. B.K. positive; sedimentation rate 76mm. (Westergren). Figure 6: Tomography. Big cavity in the right apex and beyond it a smaller one within exudative process.

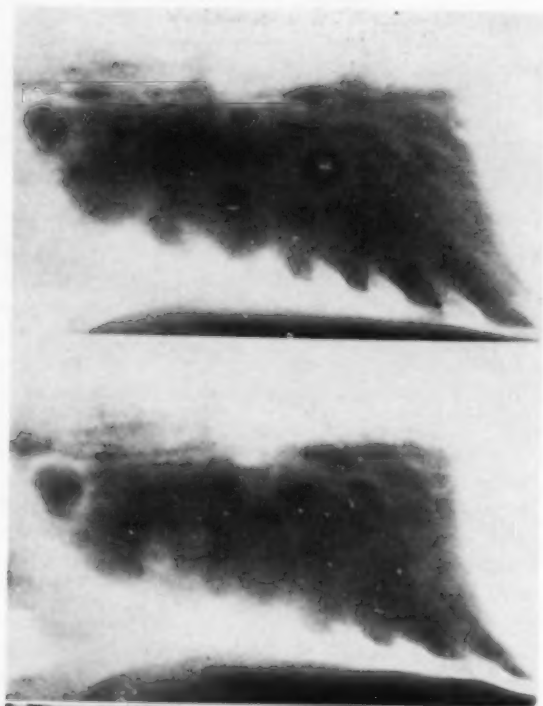


FIGURE 6

Figure 6: M. C., 13 years old, male. October 20, 1955. Right side pulmonary tuberculosis. Infiltrations with cavitations in the right upper lobe. B.K. positive; sedimentation rate 76mm. (Westergren). Figure 6: Tomography. Big cavity in the right apex and beyond it a smaller one within exudative process.

TABLE IV  
RADIOLOGICAL RESULTS

	Number of Cases	Cured	Improved	No Change	Deter- iorated
Fresh tb:					
Nodules or infiltrations	14	8	6	—	—
Cavities	10	6	4	—	—
Chronic tb:					
Nodules or infiltrations	15	—	6	9	—
Cavities	12	1	5	6	—

treatment on different forms of changes, such as nodules, infiltrations, and cavities in fresh and chronic processes. Striking is the fact that the nodules and infiltrations in fresh cases react more promptly to the treatment than the cavities (Figures 3-10). In chronic cases all forms of tuberculous processes react in equal measure to the treatment. The effects of the treatment in fresh cavities were as follows: small cavities closed, big ones either diminished so that only rest cavities remained or were changed into cystic bullae. It is to be emphasized that the results achieved by the hormonal treatment were the same after two or after three months; i.e., that the chief results were reached after two months of treatment (Table V). From the radiological point of view, the administration of the hormones after the first two months is without great value. The percentage of failures grew in direct proportion with the age of the pathological changes. In chronics almost no effect of the hormonal treatment could be observed.

3. *Complications:* As to complications, in only one case did we meet with such severe phenomena as to cause us to discontinue the treatment. In a woman, aged 47, with exudative pulmonary tuberculosis, sugar up to 3 per cent appeared in the urine after one month of treatment with ACTH. At the same time the blood sugar was within normal limits. ACTH was discontinued and after 10 days no more sugar was found in the urine. It is worth noting here that in spite of the appearance of sugar in the urine, the lung condition had improved considerably. In another patient, aged 62, who had received hormone treatment for three and one half months,

TABLE V  
COMPARISON BETWEEN RESULTS ACHIEVED BY HORMONAL TREATMENT  
IN 2 MONTHS AND 3 MONTHS

	Length of Hormonal Treatment	Number of Cases	Cured	Improved
Nodules or infiltrations	2 months	5	3	2
	3 months or more	9	5	4
Cavities	2 months	4	2	2
	3 months or more	6	3	3

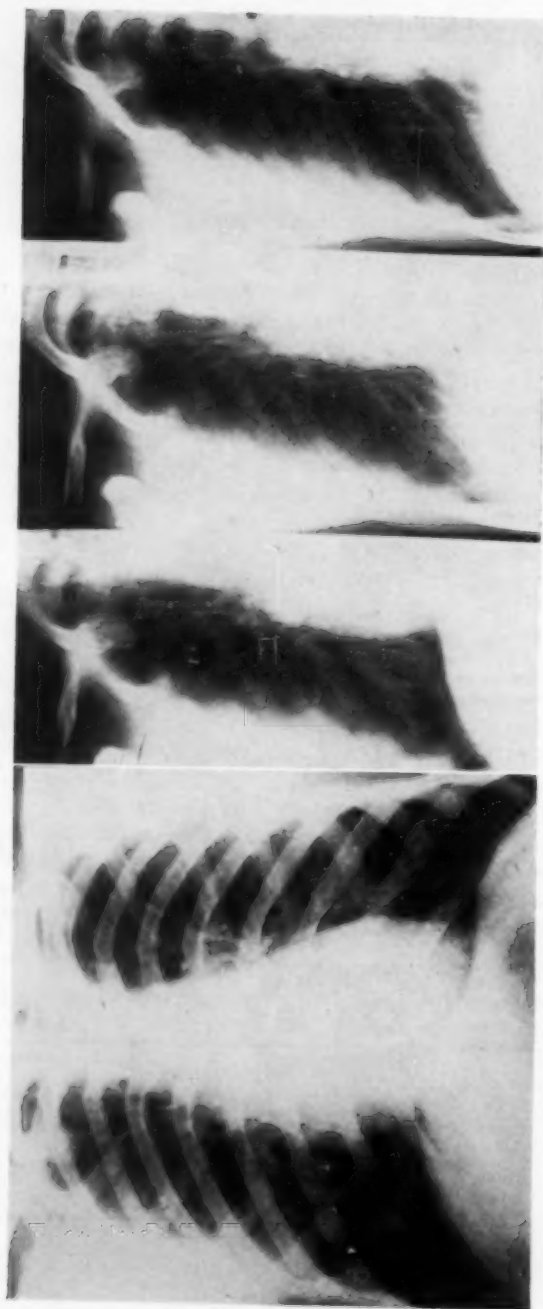


FIGURE 7

Figure 7: M. C., February 14, 1956. After three months of cortisone treatment: closure of cavities; B.K. negative; sedimentation rate 6 mm.; gain in weight 6 Kg. Figure 8: Tomography of the same case. No signs of cavitations. Marked resorption of infiltrations.



signs of osteoporosis in the lumbar spine, accompanied by severe pain appeared two months after termination of the treatment. After six weeks' therapy with testosterone, the above described complication disappeared. This case taught us to administer 25 mg. testosterone, one injection per fortnight, to each patient who is given hormones for more than two months. Later on we also found this indication in relative literature.

In a man, aged 29, whose blood pressure had been kept within normal limits (120/85), it suddenly went up to 150/100 in the seventh week of treatment with cortisone. After one weeks' discontinuation of this drug, the blood pressure went down to normal. In a woman, aged 65, with blood pressure 195/80 before initiation of treatment, the blood pressure went up to 270/110 after ten days' treatment with hormones. Two weeks after discontinuation of hormones and administration of reserpine, the blood pressure dropped to 180/80 and remained at this level.

It is also worth putting down that some patients complained of sleeplessness during and mainly at the beginning of treatment. A diminution of the hormone dose always resulted in disappearance of this complaint. In no case did we find changes of the blood electrolytes and in only the one above mentioned sugar was found in the urine. Blood sugar values were always within normal limits. There was no case of psychosis.

*Contraindications:* Patients suffering from diabetes mellitus, (although here exceptions may be made), hypertension, psychoses, ulcer of the digestive tract, uremia, and degenerative changes of the kidneys should be, in our opinion, considered as contraindicated against treatment with these hormones.

#### *Comment*

The papers of Even, Houghton, Spain, Grant, Johnson and Sors on the value and the methods of hormonal treatment in tuberculosis that have



FIGURE 9



FIGURE 10

*Figure 9:* L. A., 19 years old, female. January 12, 1956. Big atelectasis in the right middle field. Mantoux: strongly positive; B.K. negative; sedimentation rate: 46mm. (Westergren). Tuberculous inflammation (anatomically proved) of bronchial mucosa in the entrance to the apical segment of the right lower lobe. *Figure 10:* March 20, 1956, after 2 months of treatment with cortisone: clearance of the lung field; B.K. negative; sedimentation rate: 11mm. (Westergren); gain of weight: 10 Kg.

been recently published, try to explain the effect of ACTH and cortisone as causing the disappearance of the exudative changes which, from the histological point of view, are non-specific. In this sense, the effect of the hormones seems more striking and speedy compared to the one achieved by antimicrobial treatment alone. By diminishing the capillary permeability in the inflammatory region, the local oedema and the permeability of cells are diminished. ACTH and cortisone limit and hinder the exudative process without causing growth of fibrous tissue. It seems to us impossible to explain the action of ACTH and cortisone merely by stating its dilatory effect on the inflammatory reaction. Sors and Even express the opinion that ACTH and cortisone limit the action of antibiotics. It may be that this phenomenon results from a freer and easier penetration of Koch bacilli into the tuberculous focus which is not surrounded by perifocal changes. As is well known; antibiotics have, in addition to their bactericidal action, also a direct influence upon the growth of fibrous tissue. The accelerated absorption of the perifocal exudative changes hinders the antibiotics in the organization of fibrosis in this area. Therefore the fibrosis is confined and concentrated in specific changes only. Even is of the opinion that both ACTH and cortisone have a direct influence on the tubercle bacillus. The hormones invigorate its metabolism and influence its growth, in this way they render it more susceptible to the attack of the antibiotics. Of special interest is the opinion of Keller who believes that all the clinical symptoms, appearing in the general condition of the tuberculous patient, including loss of appetite, weakness, cachexia, hypotonia, trouble in the digestive tract, have a close connection with the functional disorders in the adrenals which accompany tuberculosis.

Guiseppe and Bassoli (May, 1955) point out that the elimination of 17-ketosteroids in the urine of tuberculous patients is diminished. This phenomenon is particularly striking in chronic patients. Thus the administration of ACTH and cortisone will improve the impaired function of the adrenals and will influence the tuberculous process.

It appears that as yet there are no sufficient scientific explanations as to the way hormones affect tuberculosis. One thing is certain, that the main influence is the same as in other diseases: anticongestive and antiflogistic effects, in other words, antiexudative and antifibroblastic.

#### SUMMARY

Twenty-nine cases of pulmonary tuberculosis, of whom 14 were recent, nine were chronic with exacerbation and six were chronic without exacerbation received hormonal treatment, in combination with antimicrobial drugs, during a period varying from two to three months. This treatment was also administered to persons who had pleural fluid asthma, and its complicating tuberculosis.

Cortisone and ACTH can be used safely under antibiotic coverage for the treatment of exudative fresh lesions in pulmonary tuberculosis. Exudative lesions with or without cavitation showed marked improvement compared to treatment without the addition of cortisone—time interval being the same. Identical results pertain to sputum conversion.

Exudative pleurisy and tuberculosis peritonitis improved markedly in a shorter time interval than usual. Chronic pulmonary tuberculosis did not show appreciable x-ray film changes.

In rare cases of respiratory failure and heart failure secondary to cor pulmonale, that did not respond to accepted medical treatment, the addition of cortisone improved the hopeless state.

In cases where antibiotic treatment was not tolerated, addition of cortisone made treatment possible.

The average period of cortisone and ACTH administration in pulmonary tuberculosis was two months. In cases of tuberculous exudative pleurisy treatment was limited to one month. The side effects noted were those of mild and transient glycosuria in isolated cases, mild osteoporosis in one case, and a relative transient elevation of blood pressure in a young man at the termination of treatment. No complication was noted that made interruption of treatment imperative.

#### RESUMEN

La cortisona y ACTH pueden usarse con seguridad bajo la protección de los antibióticos para las lesiones recientes exudativas de tuberculosis pulmonar. Las lesiones exudativas con o sin excavación mostraron marcada mejoría comparadas con el tratamiento sin la adición de cortisona—siendo el intervalo de tiempo el mismo.

Idénticos resultados se obtuvieron en cuanto a la conversión de los esputos.

La peluresía exudativa y la peritonitis tuberculosa mejoraron marcadamente en período de tiempo más corto que el habitual. La tuberculosis crónica no mostró cambios apreciables a los rayos X.

En raros casos de insuficiencia respiratoria y cardíaca secundaria a cor pulmonale que no respondieron al tratamiento médico usual la adición de cortisona mejoró el estado desesperado.

En casos en que el tratamiento antibiótico no fué tolerado el agregar cortisona hizo posible el tratamiento.

El término medio de tratamiento con cortisona y ACTH en la tuberculosis pulmonar fué de dos meses. En casos de tuberculosis pleural exudativa el tratamiento se redujo a un mes. Los efectos colaterales encontrados fueron una glucosuria moderada y transitoria en casos aislados, osteoporosis y en un caso al final del tratamiento y una elevación relativa temporal de la presión sanguínea.

#### ZUSAMMENFASSUNG

Cortison und Acth können ohne Gefahr unter antibiotischem Schutz angewandt werden bei der Behandlung frischer exsudativer Herde der Lungentuberkulose. Exsudative Herde mit oder ohne Kavernisierung zeigten ausgeprägte Besserung im Vergleich zur Behandlung ohne Zusatz von Cortison und bei gleichem Zeitabstand. Identische Resultate ergaben sich bezüglich der Entbazillierung des Sputums.

Exsudative Pleuritiden und tuberkulöse Peritonitiden besserten sich deutlich innerhalb kürzerer Intervalle als gewöhnlich. Eine chronische

Lungentuberkulose zeigte keine abschätzbaren röntgenologischen Veränderungen.

In seltenen Fällen von respiratorischem und cardialen Versagen auf Grund eines cor pulmonale, die auf entsprechende interne Behandlung nicht reagierten, besserte der Zusatz von Cortison den hoffnungslosen Zustand. Bei Fällen, in denen die antibiotische Behandlung nicht vertragen wurde, machte der Zusatz von Cortison eine solche Behandlung doch noch möglich. Die Durchschnittsperiode einer Cortison-Acth-Behandlung bei der Lungentuberkulose betrug 2 Monate. Bei Fällen von tuberkulöser exsudativer Pleuritis war die Behandlung auf 1 Monat begrenzt. Die beobachteten Nebenwirkungen bestanden in leichter und vorübergehender Glycosurie in vereinzelt Fällen, leichter Osteoporose in einem Fall und relativ flüchtigen Blutdruckerhöhung bei einem jungen Mann bei Beendigung der Behandlung. Es wurden Komplikationen bemerkt, die die Unterbrechung der Behandlung erforderlich gemacht hätten.

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## SECTION ON CARDIOVASCULAR DISEASES

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### Pulmonic Valvular Stenosis Associated with Interatrial Septal Defects

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Clinical investigation and surgical treatment of patients with valvular pulmonic stenosis and with atrial septal defects has shown frequent co-existence of the two lesions. These associated anomalies were encountered 12 times in a series of 50 patients with atrial septal defects. This group also constituted approximately 25 per cent of the patients operated upon for valvular pulmonic stenosis with intact ventricular septum. This presentation summarizes our experience with this particular combination of lesions.

Valvular pulmonic stenosis with a right to left shunt at the atrial level is the second most common cause of cyanotic congenital heart disease. The existence of left to right interatrial shunts without arterial oxygen desaturation in the presence of pulmonic stenosis is also well recognized. Several reports have suggested that right to left interatrial shunts may be secondary to increases in right atrial pressure which permit flow through a probe patent foramen ovale or that the shunt is the result of dilatation of the foramen ovale. It has been suggested that many of these communications in the septum are not true atrial defects. In patients with left to right shunts the opinion has been expressed that the pressure gradient across the pulmonary valve may often be the result of a functional stenosis rather than of true pulmonary outflow tract obstruction. In this series of 12 patients with diagnoses verified at open cardiectomy, the pulmonic valves were malformed in every instance and produced significant obstruction. In each instance the atrial septal defect was an open communication between the atria rather than a probe patent foramen ovale. All the defects were of the ostium secundum type. Some of them were fenestrated and others had the appearance of a greatly dilated foramen ovale.

The age range of these patients was three and one half to 30 years. Eight of the 12 were females. Growth and development were abnormal in seven

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who were more than one standard deviation below the mean values for height and weight for their ages. Growth and development had no clear-cut relationship either to the severity of the pulmonic stenosis or to the size and direction of the atrial shunts.

The symptoms of these patients were fatigue and decreased exercise tolerance manifested primarily by shortness of breath on exertion. Severe chronic cardiac failure was present in the oldest patient in the series. One child had a history of syncopal episodes. He had a relatively mild pulmonic stenosis and was intermittently cyanotic. Whether or not the syncope was related to the cardiac lesions is questionable. Constant cyanosis was present in three patients and according to the history had been life-long in two. Four had a history of intermittent cyanosis related to exertion. Two of these at the time of cardiac catheterization had evidence of reduced peripheral arterial saturation at rest. The other two had predominant left to right interatrial shunts with normal peripheral arterial saturation at rest. Squatting was observed in two patients only. In the patients with predominant right to left shunts the history of slow progression of the cyanosis over a long period of time was obtained.

Physical findings were dominated by signs of pulmonic stenosis. In those patients with right to left shunts it was often possible to differentiate this lesion from the tetralogy of Fallot on the basis of auscultatory findings. Characteristically a loud harsh systolic murmur of medium pitch lasting throughout systole was maximal in the second and third left intercostal spaces at the parasternal line. The murmur often radiated toward the left shoulder at the level of the second interspace. The first heart sound in the second interspace was frequently accentuated and had a "snapping" or "booming" quality. The second sound when audible was diminished. In a few instances it was clearly split. The three patients who were cyanotic at rest had clubbing of the fingers and toes.

Electrocardiographic changes of right ventricular hypertrophy were present in eight patients. These consisted of monophasic QRS complexes with tall R waves and delayed intrinsicoid deflections, depressed S-T segments and inverted T waves in precordial leads subtending the right ventricle. These changes were compatible with so-called systolic overload of the right ventricle. The changes of both incomplete right bundle branch block and right ventricular hypertrophy occurred three times. The right ventricular pressures in these patients were 40, 48 and 58 mm. Hg. Only one patient with relatively mild pulmonic stenosis showed an incomplete right bundle branch block. Her right ventricular pressure was 45 mm. Hg.; her pulmonary artery pressure was 23/13. An atrial septal defect with a large left to right shunt was the predominant lesion. Three patients with predominant right to left shunts showed P wave abnormalities consisting of tall, narrow peaked deflections. Their right atrial pressures were elevated and ranged from 10/3 to 16/6 mm. Hg.

Radiographic examination including cardiac fluoroscopy was helpful in establishing the diagnosis when post-stenotic dilatation of the pulmonary artery could be demonstrated. In the cyanotic patients right to left inter-



atrial shunts occasionally could be demonstrated by angiocardiology (Fig. 1). The vascular markings were not particularly indicative of reduced pulmonary flow, even when rather severe stenosis was present. They were definitely decreased in only two patients. On the other hand, the markings were not significantly increased except in one who had a large left to right shunt (59 per cent of total left atrial flow). A concave mid-segment in the postero-anterior projection associated with elevation of the apex of the heart was seen in four patients and suggested the possibility of infundibular rather than valvular stenosis. Both cardiac catheterization and later cardiectomy demonstrated that the stenosis was valvular.

Cardiac catheterization was done in all of these patients. Four of the children were sedated either with morphine and scopolamine or with a small amount of rectal pentothal. The Van Slyke method was used to estimate blood oxygen content. In addition to determining arterial oxygen saturation at rest and while breathing room air, oxygen content was

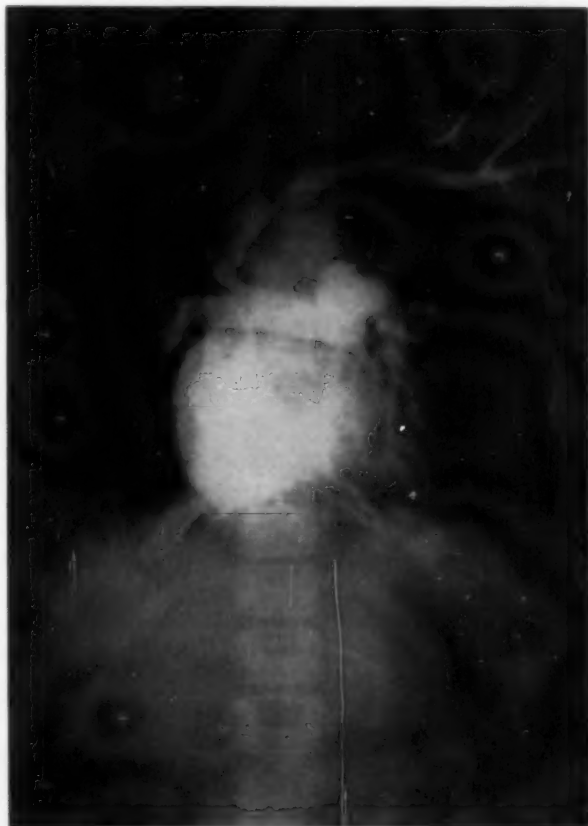


FIGURE 1: Angiocardiogram of a cyanotic patient demonstrating the right to left interatrial shunt and the poststenotic pulmonary artery dilatation.

also measured after the patient breathed 100 per cent oxygen for 10 minutes. With this technique blood is normally 100 per cent saturated with oxygen, and in addition 2.0 volumes per cent of oxygen are dissolved in the plasma. The error is approximately  $\pm 0.5$  volumes per cent. Normal values preclude a right to left intracardiac shunt.

The patients are divided into two groups according to whether the shunts were predominantly left to right or right to left. The shunt was predominantly right to left in five (Group I—Table I) and left to right in seven (Group II—Table II). Three of the five with right to left shunts (Group I) were definitely cyanotic; the other two were not obviously cyanotic at rest but had reduced arterial oxygen saturations. Right to left shunts varied from 20 to 40 per cent of total right atrial flow. Cardiac catheterization in Group I did not demonstrate significant increases in arterial oxygen content of the right atrial samples compared with vena caval samples. Right ventricular systolic pressures exceeded the systemic arterial systolic pressure in three patients by 30 to 90 mm. Hg. This was a helpful point in concluding that the ventricular septum was intact. Right ventricular end-diastolic pressures were elevated in four of the five with right to left shunts. Five of seven with left to right shunts also had some elevation of right ventricular end-diastolic pressures.

Two with right to left shunts including one with an arterial oxygen saturation of only 80 per cent had normal pulmonary artery pressures. The other three in the group with right to left shunts had abnormally low pul-

TABLE I  
PREOPERATIVE CATHETERIZATION DATA OF 5 PATIENTS WITH  
PREDOMINANTLY RIGHT TO LEFT SHUNTS

Pressures mm. Hg.												
	AGE+SEX	SYST.	R.V.	P.A.		SYST. GRAD.	ATRIAL		ART. O <sub>2</sub> SAT. %		SIZE ATRIAL DEFECT	
				Syst. - Dia.	Mean		R.A.	L.A.	Room air	100% O <sub>2</sub>		
B.L. 53-1246	7 ♀	102 <sub>5</sub> * 15	65 <sub>10</sub>	20 12	14	45	16/6 (12)	15 4	80	94	2 cm	
V.N. 56-229	12 ♀	115 <sub>60</sub>	58 <sub>8</sub>	26 13	17	32	10/3 (5)	11 <sub>2</sub>	91	100+ 0.8vol%	2 cm.	
D.W. 55-4323	13 ♂ <sup>a</sup>	125 <sub>65</sub>	155 <sub>5</sub>	12 7		143	13/2 (5)	13/3 (6)	86		2 cm	
C.D. 56-5719	28 ♂ <sup>a</sup>	120 <sub>75</sub>	150 <sub>8</sub>	17 3	10	133	12/4 (8)	9/5 (7)	86	95	3 cm.	
M.W. 49-10361	30 ♀	100 <sub>60</sub>	190 <sub>10</sub>	15 5		175	12/2 (6)	12/2 (6)	82		5 cm.	

( ) = mean pressures

\* = left ventricular pressures

monary artery pressures. They were also the ones with the highest right ventricular pressures and had systolic gradients between the right ventricle and the pulmonary artery ranging from 133 to 175 mm. Hg.

Three children with definite valvular pulmonic stenosis but with left to right shunts varying from 50 to 66 per cent of total left atrial flow had only moderate elevation of right ventricular pressures and normal pulmonary artery pressures. Three others in the same group with systolic gradients between the pulmonary artery and right ventricle of 71 to 78 mm. Hg. had pulmonary artery pressures slightly less than normal for their age but still shunted from left to right. The volume of the shunt was reduced however, and ranged from 18 to 41 per cent of total left atrial flow. An arterial saturation of 94 per cent was obtained in one of these patients (L. C.). The sample after breathing 100 per cent oxygen was lost. There is therefore the possibility that she might have had a bidirectional shunt.

It was possible to catheterize the left atrium in nine of the 12 patients of this series. Right atrial pressure was greater than left atrial pressure in two with right to left shunts; in three others with right to left shunts right and left atrial pressures were essentially the same although both were higher than normal. Left atrial pressure exceeded right atrial pressure in three with left to right shunts and was essentially the same in one. The differences in most of the atrial pressure measurements were relatively

TABLE II  
PREOPERATIVE CATHETERIZATION DATA OF 7 PATIENTS WITH  
PREDOMINANTLY LEFT TO RIGHT SHUNTS

Pressures mm. Hg.												
	AGE+SEX	SYST.	R.V.	P.A.		SYST. GRAD	ATRIAL		ART. O <sub>2</sub> SAT.		SHUNT % L.A. FLOW	SIZE ATRIAL DEFECT
				Syst. Dia.	Mean		R.A.	L.A.	Room air	100% O <sub>2</sub>		
R.S. 54-10634	3 ♂		37/6	17/9	12	20	9/4 (6)	11/5	96		16	2 cm.
D.H. 55-9005	5 ♀	100/72	88/8	17/13	14	71	11/6 (9)	17/10*	96	100 + 1.8 vol%	18	1 cm.
J.B. 54-7104	7 ♀	110/70	48/8	20/9	13	28	8/4 (5)		99	100 + 2.2 vol%	50	3.5 cm.
R.L. 54-14779	7 ♀	95/65	40/7	20/11	14	20	7/4 (5)	8/3 (5)	95	100 + 0.6 vol%	59	2 cm.
R.S. 56-9537	10 ♀	125/75	45/8	23/13	16	22	9/3 (6)	15/7 (11)	97	100 + 2 vol%	66	2.5 cm.
G.P. 44-1405	18 ♂	120/75	95/8	23/4	15	72	6/2 (3)		100	100 + 1.6 vol%	40	2.5 cm.
L.C. 56-16970	22 ♀	143/77	98/10	20/8	11	78	10/4 (6)		94		41	2.5 cm.

( ) = mean pressures

\* = pulm. vein

small and in some instances may not be particularly significant.

The aim of surgical treatment must be obliteration of the shunt between the atria and the reduction of the gradient between the right ventricular and pulmonary artery pressures. Pulmonary valvulotomy and closure of the atrial septal defects were accomplished in all of these patients. In our opinion direct visual control in a bloodless operative field, as in all other types of surgery, is essential for the correction of the defects with optimum results. We have found the use of generalized body hypothermia most satisfactory in the management of these patients. Inflow and outflow tract occlusion of the large vessels with temporary exclusion of the heart permits the direct approach to the stenotic pulmonic valve. During a second period of occlusion right auriculotomy and closure of the atrial septal defect can easily be carried out (Fig. 2). Eleven of the 12 patients were prepared for open cardiotomy by this method while one was placed on the extracorporeal circuit and pump oxygenator for repair of the defects. This one was thought to have an additional interventricular septal defect. This, however, was not verified at operation. Uniformly, the pulmonic stenosis encountered was of the valvular type. The stenosis was formed by fusion of three semilunar valves into a cone-shaped structure that produced vary-

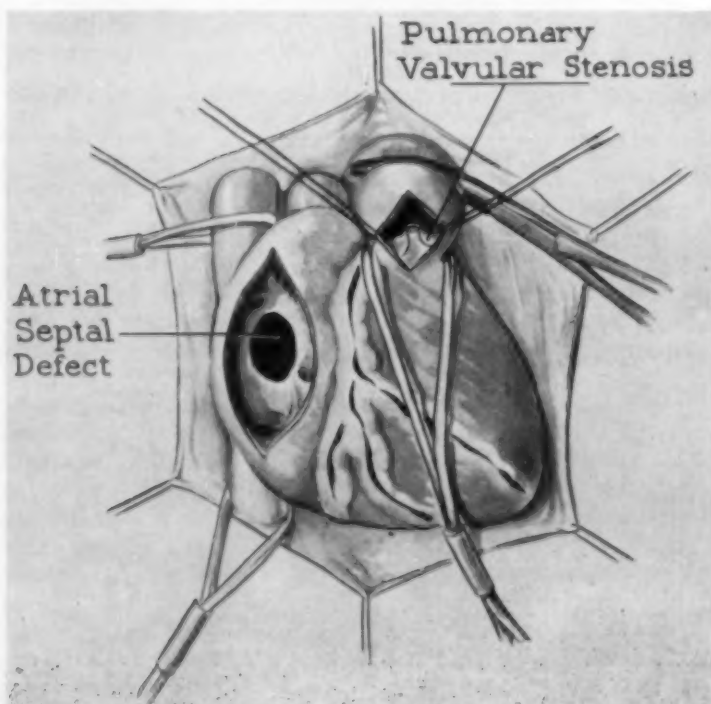


FIGURE 2: Schematic drawing showing the interatrial septal defect and the pulmonic valvular stenosis.

ing degrees of right ventricular outflow tract obstruction. Associated muscular infundibular stenosis was not observed in any of the patients even though the right ventricular outflow tract may have been narrowed in some of the patients by the severe concentric muscular hypertrophy. This occurred most frequently in the patients with arterial oxygen desaturation and very high right ventricular pressures. In no instance could the obstruction of the right ventricular outflow tract be classified as a "relative" one. Moderate to severe post-stenotic pulmonary artery dilatation was found in all patients with low or normal pulmonary artery pressures.

The interatrial septal defects were all of the ostium secundum type. The diameters varied from 1 cm. to 5 cm. We believe that most of the defects resulted from dilatation of the foramen ovale. In all instances there was free communication between the atria permitting shunts in either direction. It is inconceivable that defects of this size and type could close spontaneously after correction of the pulmonic valvular stenosis. Pulmonic valvuloplasty alone could produce some improvement in patients with right to left shunts but in others with predominant left to right shunts an increase in the volume of the shunt could occur that would make a second operative procedure necessary.

There has been no death in this series. Generally the postoperative courses were uncomplicated. In patients with large interatrial septal defects and left to right shunts mild pulmonic stenosis may be beneficial in protecting the pulmonary arterial tree from secondary degenerative change as a result of increased pulmonary flow. This may be a factor in the low mortality associated with the surgical correction of both defects. Pre-operative cyanosis was relieved. Clubbing and polycythemia have disappeared. In some of these patients, as in others with isolated valvular pulmonic stenosis studied by cardiac catheterization after pulmonary valvulotomy, a systolic pulmonic murmur may persist for a time. The pressure gradients between the right ventricle and pulmonary artery in most of them have disappeared or have been markedly reduced. Despite a complete pulmonary valvulotomy the post-stenotic pulmonary artery dilatation does persist. The murmur usually diminishes in intensity with the passage of time. Possibly this may be related to a gradual decrease of the ejectile force of the hypertrophied right ventricle postoperatively.

#### SUMMARY

Twelve patients with valvular pulmonic stenosis and either right to left or left to right interatrial shunts have been reported. The direction and volume of the interatrial shunt is ultimately a function of the severity of the valvular pulmonic stenosis. Both defects were corrected in all of these patients by open cardiectomy, using hypothermia in 11 and a pump oxygenator in one. There were no deaths. Since the most common associated defect in patients with valvular pulmonic stenosis is an atrial septal defect, atrial exploration is indicated in all patients undergoing surgery for valvular pulmonic stenosis. A method should be used which will permit correction of both defects at the same operation by open cardiectomy.

## RESUMEN

Se presentan doce enfermos con estenosis pulmonar valvular y con comunicaciones interatriales ya de derecha a izquierda o inversas. La dirección y volumen de las intercomunicaciones atriales es en último análisis en función de la severidad de la estenosis valvular pulmonar. Ambos defectos fueron corregidos en todos estos enfermos mediante cardiotoromía abierta, usando hipotermia en once y oxigenador de bomba en uno.

No hubo muertes. Puesto que el defecto más común que se asocia con la estenosis valvular pulmonar es el defecto septal atrial, la exploración atrial está indicada en todos los enfermos que se someten a la cirugía por estenosis valvular pulmonar. Debe usarse un método que permita la corrección de ambos defectos durante la misma operación por cardiotoromía abierta.

## ZUSAMMENFASSUNG

Es wird berichtet über 12 Patienten mit pulmonaler Klappenstenose und intraatrialem Rechts-Links- oder Links-Rechts-Shunt. Die Richtung und das Ausmass des interatrialen Shunts sind letzten Endes eine Funktion der Schwere der pulmonalen Klappenstenose. Beide Schäden wurden bei sämtlichen Patienten mittels offener Cardiotoromie behoben und zwar unter Anwendung der Unterkühlung bei 11 Kranken und einer Pumpe und Oxygenator bei einem Kranken. Todesfälle kamen nicht vor. Da der am häufigsten bei Kranken mit pulmonalen Klappenstenosen gemeinsam damit vorkommende Fehler in einem Vorhofs-Septum-Defekt besteht, ist eine Untersuchung des Vorhofes bei allen Kranken angezeigt, bei denen ein Eingriff wegen pulmonaler Klappenstenose vorgenommen wird. Man muss sich einer Methode bedienen, die eine Behebung beider Schäden durch dieselbe Operation und mittels offener Cardiotoromie ermöglicht.

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# The Hemodynamic and Clinical Characteristics of Rheumatic Aortic Stenosis

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The recent advances in the surgical treatment of aortic stenosis<sup>1</sup> have necessitated a more precise evaluation of the disease, especially with regard to its severity in any given patient. Clinical judgment of severity has been based on certain well-defined symptoms and signs.<sup>2, 3</sup> Whether this judgment is adequate to assess the patient as a candidate for surgery is by no means certain.<sup>4</sup> Left heart catheterization provides a method for defining the physiologic significance of the obstruction at the aortic valve, by measuring the pressure gradient across the valve during systole.<sup>5, 6</sup> When this information is combined with a flow measurement, estimated by simultaneous right heart catheterization, the degree of stenosis can be defined more accurately than previously.<sup>7</sup>

The purpose of this paper is to present the clinical and physiologic data from a group of patients with aortic stenosis, and attempt a correlation of these findings.

## Material

Forty-five patients with clinically identifiable aortic stenosis and no other valvular lesion were selected for this study. In 41, the lesion was believed to be rheumatic, although only 10 had a clear-cut history of rheumatic activity in the past, while in four it was on a congenital basis. Forty of the patients were men; five women. The age range of the group was 14 to 62 years. In 39 cases transaortic commissurotomy was performed and the surgeon's description\* of the valve confirmed the presence of a tight stenotic lesion.

## Method

History, physical examination, electrocardiogram, and cardiac x-ray film and fluoroscopy studies in postero-anterior, oblique and lateral views with barium swallow, were obtained in all cases. Simultaneous catheterization of the right and left sides of the heart was performed in all patients in the post-absorptive state. Although some patients had a history of congestive failure, no patient was judged to be in failure at the time of the study.

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\*Work done during tenure of a Public Health Research Fellowship.

\*\*All cases were operated upon by Drs. Charles P. Bailey, Henry T. Nichols, and/or Houck Bolton.

Premedication consisted of 200 mgm. of seconal and 50 mgm. of demerol. Any patient who had been taking digitalis was continued on this drug.

Although a detailed accounting of the procedure may be found elsewhere,<sup>7</sup> a brief resume will give a clearer understanding of the way in which the information is obtained. Right heart catheterization was performed in the usual way. After the catheter had been wedged to measure the pulmonary capillary pressure, it was withdrawn to the pulmonary artery and left there while the patient was turned to the prone position. A Cournand needle was placed in the brachial artery. A six inch thin-walled 18 gauge needle was then introduced, through the eighth or ninth right intercostal space near the spine, into the left atrium, according to the Fisher modification<sup>8</sup> of the Bjork technique.<sup>9</sup> A polyethylene catheter was inserted through the needle into the atrium, advanced to the left ventricle, and occasionally out to the aorta. At this point all manipulation was halted. When the heart rate, rhythm and blood pressure were stable, expired air was collected in a Tissot spirometer for three minutes, and during this period simultaneous pulmonary artery and brachial artery blood samples were withdrawn. Then pressures were recorded from the left ventricle and brachial artery simultaneously, so that the pressure gradient across the aortic valve could be measured. Pressures were then recorded as the left heart catheter was withdrawn from the ventricle to the atrium. Whenever the catheter was advanced as far as the aorta, it was withdrawn to the ventricle, so that a "pull-back" gradient could be measured and compared with the simultaneous left ventricular brachial artery gradient.

Pressure recordings were made in some of the patients by electromanometers (Sanborn) on a direct writing recorder (Sanborn). In later pa-

TABLE I  
SUMMARY OF PHYSIOLOGIC DATA

	Normal	Aortic Stenosis
1. Cardiac Index (l/m/M <sup>2</sup> )	2.6-3.6	1.2-4.4 (2.8)
2. Aortic Valve Flow cc./S.E.P. sec.)	175-250	70-317 (166)
3. L. V. Mean Systolic Ejection Pressure (mm. Hg.)	70-126	140-260 (199)
4. L.V.-B.A. Pressure Gradient (mm. Hg.)	-30 to +2	+28 to +153 (+76)
5. Aortic Valve Area (cm. <sup>2</sup> )	3.0	0.2-1.2 (0.5)
6. L.V. Total Work (Kg. M/min.)	2.9-3.9	2.4-10.1 (5.5)
7. L.V. End Diastolic Pressure (mm. Hg.)	10	0-44 (16)
8. L.A. Mean Pressure (mm. Hg.)	4-10	0-35 (12)
9. P.A. Mean Pressure (mm. Hg.)	20	8-56 (22)
10. Pulmonary Vascular Resistance (dynes/sec./cm. <sup>-5</sup> )	200	22-1050 (251)

tients in the group, a p-23D Statham strain gauge was used in conjunction with a photographic six-channel recorder (Electronics for Medicine). With the latter one can record several pressures with gauges of equal sensitivity simultaneously on a common baseline.<sup>10</sup> The zero level for pressure was taken as 5 cm. below the angle of Louis.

Blood oxygen was determined by the method of van Slyke and Neil. Oxygen content of the expired air was measured with the Pauling Oxygen Analyzer. The cardiac output was calculated by the direct Fick method. Pressure gradients were measured by planimetric integration of the area between the left ventricular and brachial artery pressure curves; tracings of the curves were superimposed for this purpose when the recordings were not on a common baseline (Sanborn recorder). Valve flow and area, pulmonary resistance, and ventricular work were calculated by modification of the formulae of Gorlin and Gorlin.<sup>11</sup>

$$\begin{aligned}
 \text{A. V. F. (cc./S. E. P. sec.)} &= \frac{\text{C. O.}}{\text{S. E. P.} \times \text{H. R.}} \\
 \text{A. V. A. (cm.}^2\text{)} &= \frac{\text{A. V. F.}}{44.5 (\text{L. V. s.m.} - \text{B. A. or A. O. s.m.})} \\
 \text{P. V. R. dynes. sec. cm.}^{-5}\text{)} &= \frac{(\text{P. A. m.} - \text{L. A. m.}) \times 1332}{\text{C. O. (m.l./sec.)}} \\
 \text{L. V. (Kg.M./min.)} &= \frac{(\text{C. I.} \times 1.055) (\text{L. V. s.m.} \times 13.6)}{1000} \\
 \text{t. w.} & \\
 \text{A. V. F.} &= \text{aortic valve flow} \\
 \text{A. V. A.} &= \text{aortic valve area}
 \end{aligned}$$

S. E. P. (sec.) = systolic ejection period  
 C. O. = cardiac output (l./min.)  
 H. R. = heart rate per minute  
 L. V. = mean systolic ejection pressure of the left ventricle  
 s. m.  
 B. A. (or A) s. m. = mean systolic brachial artery or aortic pressure

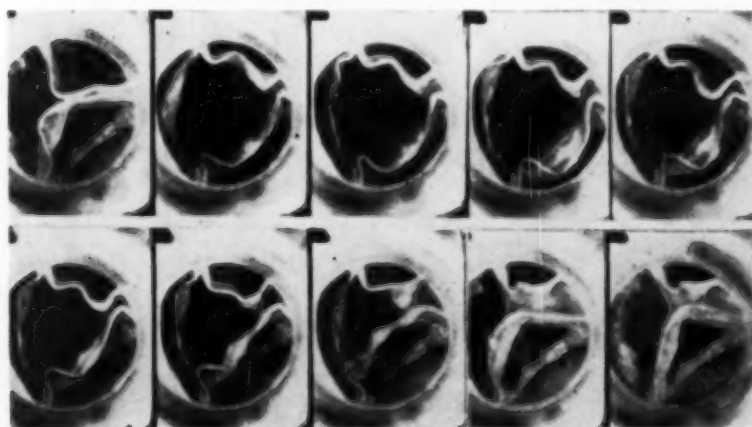


FIGURE 1A: Cinematophotograph of a perfusion of a normal aortic valve. Note size of valve orifice at height of systole in insert 3rd from left. (Top) (Courtesy I. K. R. Macmillan, British Heart Journal Vol. 17, p. 56).

P. V. R. = pulmonary vascular  
resistance  
(dynes/sec./cm.<sup>2</sup>)

P. A. = mean pulmonary artery pressure

L. A. = mean left atrial pressure

L. V. = total left ventricular  
work  
t. w.

C. I. = cardiac index (l./min./M<sup>2</sup>)

An evaluation was made of a number of cardiac clinical symptoms and signs, independently of knowledge of the catheterization figures. An attempt was made to grade (basis 0 to 4) the murmurs and the symptoms of dyspnea, angina and syncope.

### Results

The normal physiologic findings and those found in our cases of aortic stenosis are summarized in Table I.

The cardiac index and the aortic valve flows tend to be below normal for the group as a whole. The former average 2.81/m/m<sup>2</sup> with a range of 1.2 to 4.4, while the aortic valve flows average 166 cc./S.E.P., with a range of 70 to 317.

In an individual with a normal aortic valve, the aortic and left ventricular pressures are practically identical during ejection (Fig. 1). In aortic stenosis, the ventricular systolic pressure is consistently elevated and greater than the aortic (or brachial artery) systolic pressure. This gradient of pressure is the constant physiologic abnormality in aortic stenosis, ranging between 28 and 153 mm. Hg. in this series (Fig. 2).

The aortic valve areas were greatly reduced, falling below 1.2 cm.<sup>2</sup> and

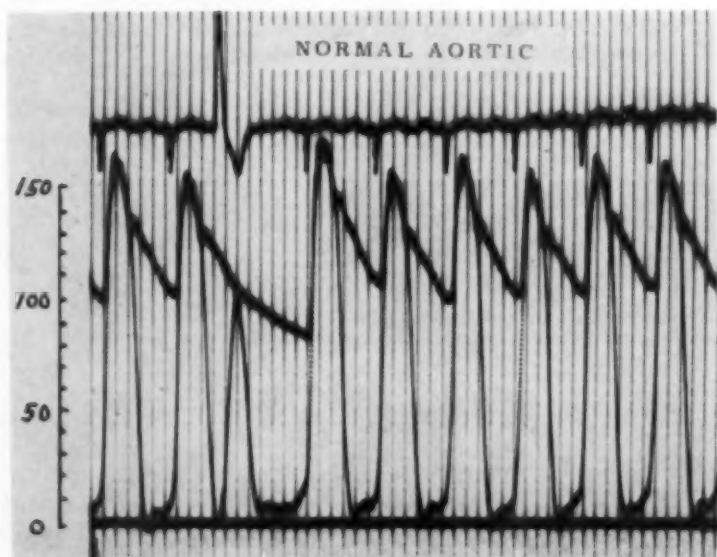


FIGURE 1B: Left ventricular and aortic pressure tracings simultaneously recorded in an individual with a normal aortic valve. Note identical pressures during the systolic ejection period.

TABLE II  
AORTIC STENOSIS (45) CASES—PHYSICAL FINDINGS

Aortic Murmurs	
Systolic	45
Diastolic	15
Aortic Second Sound	
Absent	26
Diminished	17
Normal	2

averaging 0.5 cm.<sup>2</sup> for the group. This represents  $\frac{1}{3}$  of the estimated normal aortic valve area of 3.0 cm.<sup>2</sup>

Total left ventricular work was generally increased up to two to three times normal. In several patients it was low or within normal limits, despite severe obstruction due to a marked reduction in the cardiac index.

Patients with aortic stenosis show an abnormal physiologic response to exercise. As reported previously<sup>12</sup> there is frequently an inadequate rise in the cardiac output during stress (Fig. 3). The pressure gradient and flow across the valve may or may not increase. The stroke of work of the left ventricle hence may change only slightly, certainly less than in the normal individual performing the same exertion as judged by the oxygen consumption (Fig. 4).

The left ventricular diastolic pressure was elevated above the normal of 10 mm. Hg. in 25 patients, being as high as 44 mm. Hg. The left atrial pressure reflected this elevation, particularly at the end of diastole in a giant "a" wave.

In 12 patients the pulmonary artery pressure was moderately elevated. Pulmonary hypertension was observed in four of the six cases who were in heart failure at the time of admission, although catheterized at a time when they were judged no longer in failure, and in an additional eight of 11 cases who gave a history of failure in the past. In these patients elevations of the pulmonary vascular resistance were observed.

We are not presenting in this paper any of the results of our analysis of the severity of clinical symptoms on a graded basis. This analysis was performed for the purpose of trying to correlate the symptoms and the physiologic data. No such correlation was obtained, with single symptoms and single physiologic parameters, or combinations of each. Since this was the only purpose of the grading, the presentation of the statistics on the number of patients with each grade of each symptom would be of no value.

Exertional dyspnea was the most frequent cardiac complaint, occurring in 78 per cent of the cases (Fig. 5). Nocturnal dyspnea occurred in six patients. Angina, classically precipitated by exertion with or without typical radiation, appeared in 24 (56 per cent). Syncope or vertigo was a complaint in 40 per cent. Eleven patients gave a history of failure in the past.

On physical examination all had a harsh aortic systolic murmur. A faint diastolic murmur was heard in 15. The second aortic sound was

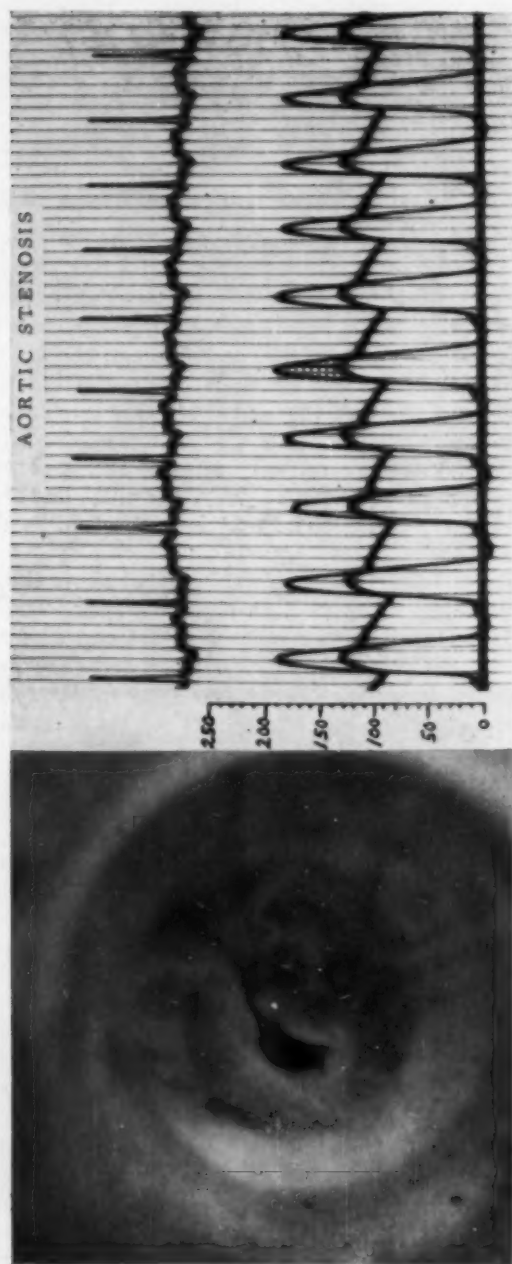


FIGURE 2A

*Figure 2A:* Cinematophotograph of a perfused aortic valve at height of systole in patient with aortic stenosis. Note fusion of leaflets and small orifice. Compare with Figure 1A.—*Figure 2B:* Left ventricular and aortic pressures in aortic stenosis. Shaded area represents systolic pressure gradient.

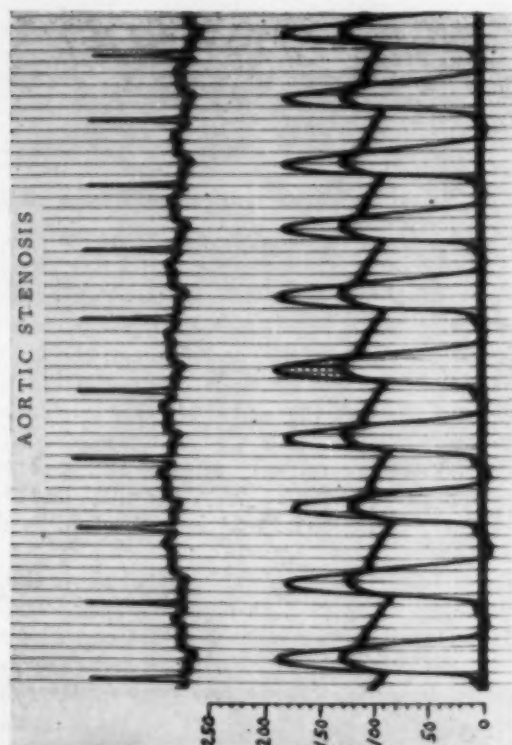


FIGURE 2B



TABLE III  
AORTIC STENOSIS (45 CASES)

Cardiac Size	
Normal	7
Borderline	6
Plus 1	17
Plus 2	13
Plus 3	2
Aortic Valve Calcification	41 (91 per cent)

normal in only two. One of these had a congenital lesion. In the remainder the second sound was either much diminished (17 cases) or absent (26 cases). On admission six patients (not included in the 11 mentioned at the end of the last paragraph) had signs of congestive heart failure, as evidenced by basal pulmonary rales and/or peripheral edema.

Left ventricular hypertrophy or strain was the most frequent finding in the electrocardiogram (33 cases). Left bundle branch block was seen in three. In four tracings the ST-T changes were thought due to digitalis therapy alone, while non-specific T wave abnormalities were observed in three instances. In one patient the electrocardiogram was suggestive of coronary artery disease.

The roentgenologic findings revealed a normal cardiac size in seven. There was a suggestion of left ventricular hypertrophy, in the form of rounding of the lower left cardiac border, but no over-all enlargement. Borderline enlargement was seen in six instances. The heart was moderately enlarged, 1-2 plus, in 20 cases and considerably enlarged, 3 plus, in only two. It should be noted that no Grade IV cardiac enlargement was seen.

Aortic calcification was observed roentgenographically in 29 patients, and found in an additional 12 at surgery. Planigrams were done in only a few cases, but probably would have increased the number of positive x-ray findings, if they had been done routinely.

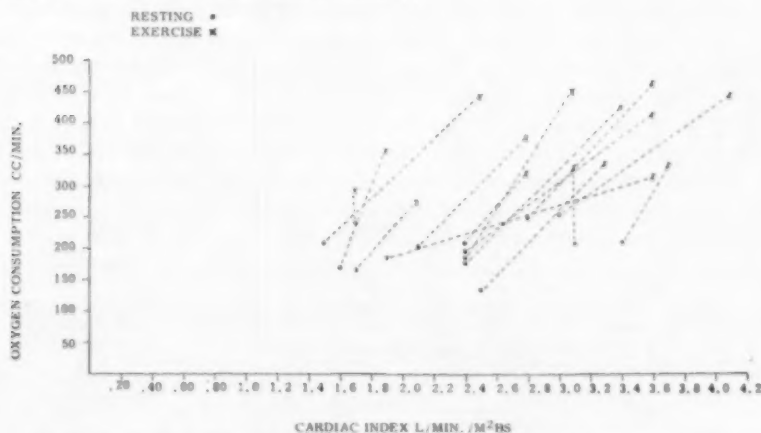


FIGURE 3: Effect of exercise upon the cardiac index in aortic stenosis.

### Discussion

In any consideration of the physiologic data in aortic stenosis the most significant findings needing discussion are the low cardiac output and the pressure gradient across the valve.

The commonest cause of a decreased output in heart disease is cardiac failure, especially left ventricular failure. This cannot be excluded as a factor in any of our cases, especially where clinical failure had been present in the past. However, some patients with no history of failure had just as low an output. One could say that they were examples of subclinical failure, but it is also possible that the valvular obstruction *per se* may contribute to the low output.<sup>12</sup>

In order for the output to be maintained at normal levels, with a narrowed orifice, the ejecting force must increase. One might expect that this force could increase in proportion to continued narrowing at the valve. Actually, one finds that the systolic ejection pressure rarely rises above 250 to 300 mm. of Hg.<sup>16</sup>; presumably the myocardium is incapable of generating any higher pressure. If one wishes to define this as failure, then we find ourselves dealing in semantics. The fact is that this same myocardium, 10 days after the valve has been opened, has been shown in some cases capable of increasing the output.<sup>17</sup>

Even where the resting output is normal, there may be a failure to increase the output normally on exercise. Here again myocardial failure or valvular obstruction or both may play a role.

The rise in systolic pressure in the ventricle is the means by which this chamber maintains the cardiac output. It is this rise, coupled with the valvular obstruction which leads to the pressure gradient across the valve, which is so characteristic of dynamic aortic stenosis. The rise in pressure is responsible for the rise in total left ventricular work, since this factor is included in the formula for total work. A marked fall in the cardiac output could result in a lesser rise or even a fall in work, and it is certainly true that in severe heart failure, the total work will fail, as the left ventricle becomes incapable of producing a marked rise in systolic pressure.

The increase in work may be looked on as a cause of the resulting hypertrophy of the myocardium. This in turn may enable the ventricle to raise the systolic pressure still higher. However, the degree to which hypertrophy may go on is limited by the coronary blood flow. Certain it is that it does not go on *ad infinitum*. The aortic obstruction imposes some limits on the perfusion pressure available for the coronary vessels, and also on the output available for them. Moreover, the increased systolic resistance to flow in the hypertrophied muscle cuts down on whatever coronary flow

TABLE IV  
AORTIC STENOSIS—ELECTROCARDIOGRAM FINDINGS (45 CASES)

Left Ventricular Hypertrophy and Stain	33
Left Bundle Branch Block	3
Digitalis Effects	4
Non-specific Changes	3
? Coronary Artery Disease	1

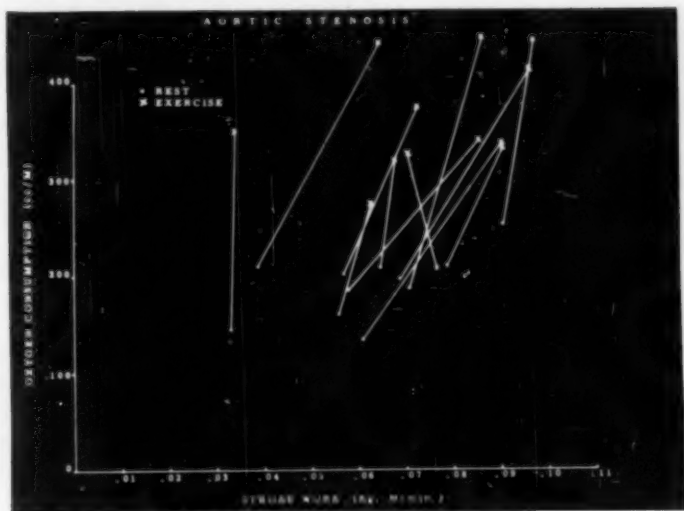


FIGURE 4: Effect of exercise on the stroke work of the left ventricle in aortic stenosis.

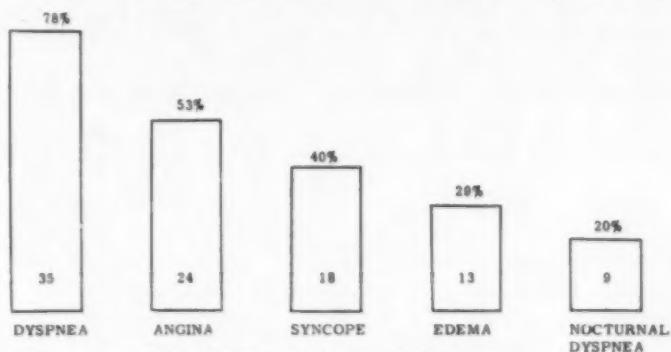


FIGURE 5: Incidence of symptoms.

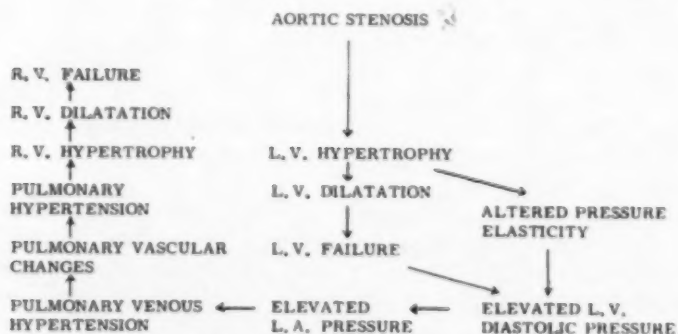


FIGURE 6: Patho-physiologic changes in the course of aortic stenotic valvular disease.

normally does occur in systole. For these reasons hypertrophy is not a process which can occur indefinitely.

It is doubtful if one should wish it to be so, since the thickened muscle does not have normal distensibility. As the pressure-volume relations of the myocardium alter as a result of the hypertrophy the end diastolic pressure in the ventricle rises.<sup>7</sup> The left atrial pressure likewise must rise to permit blood to flow into the less distensible ventricular chamber. This is most noticeable at the end of diastole, when a giant "a" wave is seen in the left atrial pressure tracing. A similar phenomenon has been observed in the right atrial pressure curve in cases of pulmonic stenosis or other cause of right ventricular hypertension.<sup>13</sup>

Any discussion of an elevated left atrial pressure leads backwards to a mention of pulmonary hypertension. Certainly this is a cause of elevated pulmonary vascular pressure and resistance. Such an elevation, whether acute as in sudden left ventricular failure, or chronic due to the diminished distensibility of the left ventricular myocardium, may result in anatomic pulmonary vascular changes.<sup>14</sup> These in turn elevate the pulmonary artery pressure still further as long as the right ventricle maintains its output. Later, when the right ventricle can no longer maintain this output, failure of this chamber occurs and is manifested by hepatomegaly and peripheral edema.

The diagram shown in Figure 6 summarizes these patho-physiologic changes in the course of stenotic aortic valvular disease.

The three chief clinical manifestations of the disease also merit brief comment.

Dyspnea, primarily exertional, is the commonest symptom. Is this truly due to left ventricle failure? If one considers failure the inability of the heart to meet the demand of the tissues, then this must be considered to be failure. However, as pointed out above, we believe it possible for the left ventricular diastolic pressure, the atrial pressure and the pulmonary venous pressure to rise, early in the course of the disease, simply because of the hypertrophy of the left ventricle. When this occurs, pulmonary congestion and exertional dyspnea may ensue, even though the myocardium has not truly failed, except in the face of the stenotic valve. At this stage surgical opening of the valve would probably give the most satisfactory results (assuming that calcification was not so massive as to prevent adequate mobility), since the myocardium would still be in reasonably good condition. Perhaps, even earlier surgical intervention, in the absence of symptoms, before much hypertrophy has occurred, would be preferable, when the mortality of surgery is sufficiently low to warrant intervention at this stage of the disease.

Angina in these patients represents a disproportion between the coronary blood flow and the demands of the hypertrophied myocardium. Atherosclerosis probably plays only a small part in the production of this symptom, although if present to any degree would undoubtedly aggravate the coronary insufficiency. The hypertrophied muscle mass has probably outgrown its coronary vasculature. The work of the left ventricle has

doubled or tripled while cardiac output may be normal or low; hence the coronary flow is likewise normal or below. Herein lies the major reason for the disproportion. A minor additive factor is probably the increased systolic resistance to flow in the muscle itself, decreasing whatever systolic flow does occur in the myocardium.

Syncope has been explained by Marvin and Sullivan<sup>15</sup> as due to a hyperactive carotid sinus. However, the disappearance of this symptom after cardiac surgery makes this explanation unlikely.<sup>17</sup> It seems more likely that an inadequate cerebral blood flow secondary to an inadequate rise in cardiac output with exercise is the major cause of effort syncope in aortic stenosis. Such cerebral blood flow measurements in patients with this disease under conditions of rest and exercise, have not been made, but would be worth doing in the investigation of this problem. The findings after exercise, when the cardiac output is measured, certainly point in this direction.

Finally, some reasons for our failure to correlate symptoms with the pathologic physiology should be offered. We had expected that perhaps the degree of dyspnea would correlate with the left ventricular diastolic pressure, or the pulmonary artery pressure or perhaps inversely with the cardiac output; or that angina would be related to left ventricular work, or aortic valve flow or a combination thereof; or that the severity of syncope attacks might show a relation to the cardiac output or the aortic valve area. Why were these expectations not fulfilled?

First, the symptomatology was graded on the basis of the patient's subjective description of a period in his life covering perhaps six months or longer prior to admission, while the physiologic data were obtained at a relatively instantaneous moment in his hospitalization. Second, the symptoms described the individual's response to various activities, while the catheterization data were obtained at rest in the majority and in a small number of cases during exercise, but the relationship of this exercise to daily activity is not known. Third, the actual grading of symptoms is probably subject to serious error, since individuals may make different demands on their hearts even where the pathology is similar. The attempt to grade the symptoms or the physiologic data produced several groups with small numbers of patients. Finally, we must admit that the physiologic data fail to evaluate the myocardial factor, which may be as important as the valvular obstruction in the production of the pressure gradient and hence greatly influence the magnitude of the cardiac output.

#### *Conclusions*

It would appear that once a patient with aortic stenosis develops dyspnea, angina or syncope, or some combination of these, a physiologically significant degree of obstruction is present and the aortic valve area is less than 1 cm.<sup>2</sup> one-third of normal. That a critical aortic valve area exists was suggested by others.<sup>16</sup> Once the valve orifice has been reduced to this critical size, then the type and degree of symptoms may be variable. Electrocardiographic and x-ray evidence of left ventricular enlargement only

confirm the physiologic significance of the lesion. This concept is confirmed also by the physiologic and clinical changes that follow surgery for this lesion. After aortic commissurotomy, Smith and associates<sup>17</sup> found in 17 patients in this series that although the pressure gradient is only occasionally eliminated (in two cases) and physiologic obstruction is still present, the symptom triad of dyspnea, angina and syncope is relieved in those cases where the calculated post-operative valve area has been brought above 1 cm.<sup>2</sup>

#### SUMMARY

1. The physiologic and clinical characteristics of aortic stenosis are presented in 45 cases studied by combined heart catheterization, 39 of which came to surgery.

2. A constant finding is the presence of a systolic pressure gradient at the aortic valve. The aortic valve flow is generally reduced, and the average valve area was calculated to be 0.5 cm.<sup>2</sup> (normal 3.0 cm.<sup>2</sup>).

3. The clinical triad of dyspnea, angina and syncope or some combination of these appear when the valve area is reduced below 1.0 cm.<sup>2</sup> The lack of correlation between the physiologic data and the severity of symptoms is discussed.

*Acknowledgments:* The authors wish to express their appreciation to Mr. George Raber and the Misses Betty Underwood, Ruth Freeman and Evelyn DeSimone for their technical assistance, and to the other members of the catheterization team.

#### RESUMEN

1. Se describen la fisiología y las características clínicas de la estenosis aórtica en 45 casos estudiados por la combinación de la cateterización cardíaca. De ellos, 39 se sujetaron a la cirugía.

2. Un hallazgo constante es la presencia de un gradiente a la presión sistólica en la válvula aórtica. El flujo de la válvula es generalmente reducido y el término medio de área de la válvula se calcula de 0.5 cm. 2 (normal: 3.0 cms. 2).

3. La triada clínica de disnea, angina y síncope o alguna combinación de estos, aparece cuando la válvula se reduce hasta abajo de 1.0 cm. 2. La falta de correlación entre los datos fisiológicos y la gravedad de los síntomas es motivo de consideraciones.

#### RESUME

1. Les auteurs rapportent, les caractéristiques physiologiques et cliniques de la sténose aortique dans 45 cas, étudiés avec cathétérisme cardiaque. Parmi eux, 39 furent opérés.

2. Une constatation constante est donnée par le gradient de la pression systolique au niveau de la valvule aortique. Le débit de cette valvule aortique est généralement réduit, la surface valvulaire moyenne représentait selon leurs calculs 0,5 cm2 alors que la normale est de 3 cm2.

3. La triade clinique dyspnée, douleur constrictive et syncope, ou une combinaison quelconque de ces symptômes, apparait lorsque la surface valvulaire s'abaisse au-dessous de 1 cm2. Les auteurs discutent l'absence



de corrélation entre les données physiologiques et la sévérité des symptômes.

#### ZUSAMMENFASSUNG

1. Es werden die physiologischen und klinischen Merkmale der Aortenstenose dargestellt an 45 mit kombinierter Herz-Katheterisierung untersuchten Fällen, von denen 39 zur Operation kamen.

2. Ein gleichbleibender Befund ist das Bestehen eines systolischen Druckgefälles an der Aortenklappe. Die Durchströmung an der Aortenklappe ist für gewöhnlich verringert, und der durchschnittliche Klappenbereich wurde mit 0,5 qcm errechnet (normal = 3,0 qcm).

3. Die klinische Trias von Kurzatmigkeit, Angina und Kollaps oder irgendeine Kombination dieser Symptome tritt auf, sobald das Klappenareal unter 1,0 qcm verringert ist. Besprechung des Fehlens der Korrelation zwischen den physiologischen Daten und der Schwere der Symptome.

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# The Normal Phonocardiogram of the Aged\*

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The gradually increasing interest in exact knowledge of the data concerning the *senile heart* indicated the need for an exact study of phonocardiography which would indicate the limits within which the heart sounds could be considered normal. Similar studies have been made in the heart of the normal adult (Rappaport and Sprague,<sup>1</sup> Luisada et al.<sup>2</sup>) and in that of the normal child (Aravanis and Cardi<sup>3</sup>). Collateral data dealing with the electrocardiogram, the pulse rate, the heart x-ray films and the blood pressure have been collected in order to prove that the cardiovascular system of the patients was not affected by disease.

## Material and Method

In order to evaluate the heart sounds of elderly persons with clinically normal hearts, a phonocardiographic investigation was performed in 100 people between the ages of 60 and 108. The majority of them were selected from a group of 600 permanent residents at the Ann Lee Home. A few were obtained from the Troy Jewish Home for Aged and the Albany Home for Aged of the Little Sisters of the Poor. Sixty-nine were men; 31 were women. Table I shows the age distribution of the patients. The final selection was made on the basis of normal history and physical examination, normal blood pressure, normal cardiac silhouette in the roentgenogram, and the absence of definite ECG changes. Persons with a history of dyspnea, angina, coronary occlusion, or heart failure, or receiving cardiac drugs, were excluded. Thus, the possibility of significant heart disease which could influence or change the heart sounds was greatly eliminated. Most of these residents were in the Home only because of their age. A few had senile disorders which did not affect the heart.

"Stethoscopic" and "logarithmic" phonocardiograms were taken over the routine five precordial areas as described elsewhere<sup>5</sup> with a Sanborn Twin-Beam Cardiette. Simultaneous carotid pulse tracings were also recorded.

## Analysis of Data

*Phonocardiogram—Heart Sounds.* The duration of the first and second heart sounds was measured in the "stethoscopic" tracing. The first sound was measured at the apex; the second, at the base. Two measurements

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TABLE I  
AGE DISTRIBUTION

60 - 69	27 Cases
70 - 79	28 Cases
80 - 89	31 Cases
90 - 108	14 Cases

TABLE II  
DURATION OF HEART SOUNDS

Age	First Sound		Second Sound	
60 - 69	Total duration	0.182	Total duration	0.110
	Central phase	0.052	Central phase	0.042
70 - 79	Total duration	0.174	Total duration	0.109
	Central phase	0.051	Central phase	0.044
80 - 89	Total duration	0.168	Total duration	0.102
	Central phase	0.055	Central phase	0.039
90 - 108	Total duration	0.158	Total duration	0.094
	Central phase	0.054	Central phase	0.039

TABLE III  
DISTANCE BETWEEN FIRST AND SECOND SOUND

Age	Seconds	
60 - 69	0.333	
70 - 79	0.330	With a mean value for all ages 0.336
80 - 89	0.325	
90 - 108	0.320	

TABLE IV  
BLOOD PRESSURE ACCORDING TO THE AGE GROUP

60 - 69	Men	137/84	138/83
	Women	139/79	
70 - 79	Men	132/83	135/85
	Women	136/84	
80 - 89	Men	131/85	133/83
	Women	135/81	
90 - 108	Men	131/70	130/77
	Women	137/88	

Average pulse rate for all ages = 81 per minute.

Average QT Ratio = 1.02 for all ages.

were done: the total duration of each sound from the beginning to the end, and the duration of their central phase. This last measurement excludes several low-pitched vibrations both at the beginning and at the end of each sound.

The average total durations of both sounds were found to be prolonged, but not significantly so (Table II). As the age increases, the average total duration of the first sound progressively diminishes from 0.182 second, in the group 60-70, to 0.158 second, in the group 90-108. On the contrary, the average duration of the central phase of the first sound does not change significantly, although it shows a slight increase (from 0.052 for the ages 60-70 to 0.054 for the ages 90-108). The average total duration of the second sound also decreases with age (0.11 in the age group 60-69, 0.094 in that 90-108). The average duration of the central phase of the second sound decreases from 0.042 in the age group 60-70 to 0.039 in the age group 90-108.

The distance between the first and second sound (*mechanical systole*) was found slightly decreasing as the age increases, with an average value of 0.325 second (Table III).

A fourth heart sound of normal amplitude was found in 21 cases (21 per cent); in two of them, the amplitude of this sound was high but the pitch was low, so that it did not fulfill the criteria of a presystolic gallop.

A large low-pitched vibration at the end of the first sound was found in a high percentage of this group. There is the opinion that this is a vascular vibration (aortic or pulmonic).

A third heart sound of small amplitude was present in two cases (2 per cent).

*Murmurs.* No significant murmur was found in the group. This was expected on the basis of the criteria for selection. In 13 cases (13 per cent), a small systolic murmur was recorded over both the apex and the base of the heart. This was a decrescendo murmur with a regular type of vibration (musical murmur).  $A_2$  and  $P_2$  were normal.

*ECG.* None of the patients had an abnormal ECG as a result of the selection. In three, occasional auricular extrasystoles were present, and in two the P-R interval was 0.22 of a second (this may still be considered within the upper limits of normal).

*Blood pressure.* The average figures according to age and sex are shown in Table IV. It is apparent that both the systolic and the diastolic pressures decrease as the age increases, both in men and women. This fact is more pronounced among men. It should be remembered that hypertensive patients were not considered.

*X-Ray Films.* In all cases, a chest x-ray film was taken in the P-A position and in deep inspiration. It was found that, in 29 cases (29 per cent), the heart was slightly increased in size, usually because of left ventricular enlargement. However, some of the films reveal that the patient was not in deep inspiration during the exposure. Therefore, the findings are not absolutely comparable. The aorta was found to be wide and tortuous in

74 per cent of the cases. Forty-four per cent had calcifications in the aortic arch. Only 23 per cent had a normal aorta.

*Q-T Ratio.* The Q-T ratio was measured in order to see whether old people have the same values as younger persons. The average QTr for all ages was found to be 1.02. The lowest value was 0.80, and only one case had a value of 1.20.

*Pulse Rate.* The average pulse rate for all ages and for both sexes was 81 per minute. No significant difference was found between the different ages and between men and women.

*Pulse Tracing.* The carotid tracing was taken by using a small funnel, which was held by the hand against the right carotid artery. A normal pulse tracing was found in all cases. A rapid rise, a rather slow fall, and a marked dirotic wave were typical. The distance between the largest vibration of the first sound and the end of the ascending limb of the pulse was from 0.06 to 0.08 second. This confirms our findings in a previous study in cases with relative and organic aortic stenosis.<sup>1</sup> In relative stenosis, the distance between first sound and ascending limb of the pulse was about the same as that found here; in organic stenosis, it was prolonged. The peak of the pulse was rounded in 63 per cent of the cases, a fact which was considered evidence of arteriosclerosis of the aorta. An anacrotic notch was not present but, in 13 cases, a shallow depression existed in the ascending branch and was considered equivalent to this notch. The catacrotic notch was present in all cases and coincided with the second aortic sound.

*Blood Count.* A normal red blood count was found in all cases, although a tendency to higher values was encountered in a good percentage of them. Forty per cent of the cases had more than five million red cells, with a normal amount of hemoglobin. This is probably the result of chronic pulmonary emphysema.

#### Discussion

This study was made in 100 selected senile persons between the ages of 60 and 108. As a condition for the selection of the cases was the absence of high blood pressure, and the absence of any relevant change of the electrocardiogram, it is self-understood that these abnormalities were absent.

The duration of the heart sounds was measured in the phonocardiogram. The average total duration of the first sound was found only slightly prolonged in comparison with the normal adults.<sup>1</sup> As the age increased, the total duration of the sounds decreased. On the other hand, the duration of the central phase of the sound did not change with increased senility.

The average total duration of the second sound also decreased with age but, in contrast with the first, the duration of the central phase also decreased. The importance of this phase is that it is made of large, high-pitched vibrations and is the only part which is clearly audible. Therefore, one would expect shorter, more snapping heart sounds upon auscultation of subjects of advanced age.

Collateral data of interest were:

- (a) A slight tendency to a decrease of blood pressure with age.
- (b) A normal pulse rate.
- (c) A normal QT ratio in the electrocardiogram.
- (d) An average duration of mechanical systole of 0.336.
- (e) A trend toward a slight increase of red blood cells with age.
- (f) A rapid rise, a slow fall, and a high dicrotic wave in the pulse.
- (g) A slight enlargement of the left ventricle revealed by chest films.

#### SUMMARY

A phonocardiographic study was made in 100 old persons selected because of the absence of data indicating heart disease.

The heart sounds were found to slightly decrease in duration with advanced age.

Collateral data which were collected were: pulse rate, duration of ventricular systole, QT ratio, hematological, roentgenological and sphygmographic data.

The above tabulated phonocardiographic data can be used for comparison in the study of tracings of old patients presenting murmurs or other auscultatory abnormalities.

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We wish to thank Mrs. P. Hinds and Mrs. Harris for their technical assistance.

#### RESUMEN

Se hizo un estudio fonocardiográfico en 100 ancianos escogidos por su ausencia de datos indicadores de enfermedad cardíaca.

Los ruidos cardíacos se encontraron ligeramente disminuidos en su duración en la edad avanzada.

Los datos colaterales que se obtuvieron fueron: frecuencia de pulso, duración de sístole ventricular, relación QT, hematología y datos esfigmográficos.

Los datos fonocardiográficos arriba tabulados pueden ser usa dos para comparar en el estudio de los trazos de las personas ancianas presentando soplos u otras anormalidades auscultatorias.

#### RESUME

Une étude phonocardiographique fut pratiquée chez 100 personnes âgées choisies à cause de l'absence d'éléments indiquant chez elles l'existence d'une affection cardiaque.

D'après ces observations, les bruits du coeur semblent diminuer légèrement en durée avec l'âge.

Parallèlement furent recueillis des éléments concernant la fréquence du pouls, la durée de la systole ventriculaire, l'état du tracé QT, des constatations hématologiques, radiologiques et sphygmographiques.

Les données phonocardiographiques ci-dessus rassemblées peuvent être



utilisées pour l'étude des tracés des malades âgés présentant des souffles ou d'autres anomalies d'auscultation.

#### ZUSAMMENFASSUNG

Eine phonocardiographische Untersuchung wurde angestellt bei 100 alten Menschen, deren Auswahl erfolgte wegen des Fehlens von Angaben, die auf eine Herzerkrankung hinwiesen.

Es fand sich, dass die Herztöne etwas an Dauer abnahmen mit zunehmenden Alter.

Gleichlaufende Werte, die erhoben wurden, bestanden in: Pulszahl, Dauer der ventrikulären Systole, QT—Verhältnis, haematologische, röntgenologische und spychmographische Werte.

Die wie oben tabellenförmig zusammengefassten phonocardiographischen Daten lassen sich zum Vergleich verwenden bei der Untersuchung von Kurven alter Menschen, die Geräusche oder andere auskultatorische Abweichungen bieten.

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## CURRENT THERAPY

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### The Lipid Problem in Atherosclerosis

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Atherosclerosis is a disease process involving primarily the intima of the main coronary arteries, the aorta and the major arteries of the cerebrum and lower extremities. The lesions tend to be patchy and plaque-like. Symptoms are produced by occlusion of the lumen of the vessel with impairment of blood flow to the organ involved. This is usually accomplished by a progressive increase in the size of the atheromatous plaque or by the formation of a thrombus on the plaque. Occasionally the atheromatous process extends into the media with weakening of the vessel wall with aneurysm formation. Benign Monckeberg's medial calcinosis or the diffuse arteriosclerosis encountered in severe hypertension is not being considered.

Undoubtedly many factors are important in the genesis of atherosclerosis. However, there is abundant evidence that elevated levels of serum cholesterol, various classes of B-lipoproteins, and probably other lipid factors such as fatty acids and triglycerides are of paramount importance in the development of atherosclerosis and its complications. Because of the conflicting data and the numerous gaps in our knowledge concerning the metabolism of cholesterol and other lipids, many have felt that the clinician should avoid attempts to draw therapeutic implications at the present state of our knowledge. However, since more Americans die from coronary atherosclerosis alone than from all forms of malignancy combined,<sup>1</sup> it would seem imperative to ask if the practicing physician is not justified in drawing a few tentative conclusions from the mass of conflicting and inadequate data so long as these therapeutic views and conclusions are not potentially harmful to the patient and remain flexible enough to be modified as additional facts become available.

The principle evidence linking atherosclerosis with altered cholesterol metabolism is as follows: Experimental lesions can be produced in numerous laboratory animals by feeding cholesterol and by other dietary procedures. The experimental lesions are always preceded by an elevation of serum cholesterol. The lesions themselves have a high cholesterol content. If the animal's diet is altered so that serum cholesterol is reduced, the experimental lesions tend to regress. An increased incidence of atherosclerosis is observed in clinical states associated with hypercholesteremia such as xanthoma tuberosum, myxedema, diabetes and nephrosis. Indi-

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viduals who suffer myocardial infarctions early in life tend to have higher levels of serum cholesterol and lipoproteins than the general population. However, there is no direct evidence that dietary cholesterol elevates serum lipid levels or causes atherosclerosis in humans. This is probably due to the fact that total circulating cholesterol in humans is largely endogenous in origin.<sup>2</sup> There is accumulating evidence that elevated serum lipid levels, in addition to their importance, in the development of atheromatous lesions, may also be involved in the development of the major complication of atherosclerosis, namely thrombus formation. Several studies have indicated an increased clotting tendency in the presence of elevated serum lipids.<sup>3, 4</sup>

*Factors Known to Lower or Alter Serum Lipids in the Human  
Nutrition and Diet*

Knowledge is now available that enables one to understand and reconcile many of the conflicting claims of the past. Insurance studies have long indicated an increased death rate from diseases due to atherosclerosis in overweight individuals and a low death-rate from these diseases in lean individuals. Furthermore, it has been demonstrated that obese individuals who reduce their weight also reduce their expected mortality from these diseases.<sup>5</sup> Clinical studies have revealed significantly higher average levels of serum cholesterol and certain lipoproteins in overweight persons.<sup>6</sup> Weight reduction has been shown to lower these levels and positive caloric balance to elevate them even on a fat free, cholesterol free diet.<sup>7</sup> (A diet that causes the body to form fat containing highly saturated fatty acids). Increased caloric intake was not associated with elevated serum lipids if there was an equal increase in physical activity.<sup>8</sup> Others have emphasized the correlation between high dietary fat intake, elevated levels of serum cholesterol, and a high incidence of atherosclerosis.<sup>9</sup> The decreased death rate from atherosclerosis in various occupied countries during World War II, has also been attributed to the low dietary fat intake at that time. Since overweight individuals tend to ingest more calories and fat than lean individuals, it has been difficult to decide whether the state of nutrition or the increased dietary fat was the essential factor in the observed increased incidence of atherosclerosis and elevated lipid levels. A recent study in which a group of patients with atherosclerosis sustained a large weight loss while ingesting a diet extremely high in animal fat indicated that the  $S_r$  0-12 classes of B-lipoproteins are directly influenced by dietary fat intake, while the  $S_r$  20-400 fraction appears to be more directly influenced by the state of nutrition.<sup>10</sup> This, (along with other data) suggests that both obesity and dietary fat intake may be independent predisposing factors in the development of atherosclerosis. Evidence is accumulating that the type of fat ingested may be much more important than the mere quantity consumed. The ingestion of fats composed largely of saturated fatty acids such as occur in most animal fats or vegetable fats that have been hydrogenated and converted to a solid state tend to elevate serum cholesterol and lipoprotein levels while large

amounts of unsaturated essential fatty acids, such as linoleic acid, which cannot be synthesized in the body, tend to lower serum cholesterol levels.<sup>11</sup> The essential fatty acids are thought to be important in the transport of cholesterol.<sup>12</sup> Of the available vegetable oils, safflower oil and corn oil, have the highest content of linoleic acid.

#### *Female Sex Hormone*

Premenopausal women are relatively "immune" to the complications of atherosclerosis. In addition, they have lower levels of serum cholesterol and B-lipoproteins than males of comparable age and state of nutrition. Following the menopause, or after surgical castration, the female loses her protection against atherosclerosis and manifests significantly higher serum lipid levels.<sup>6, 13, 14</sup> The administration of estrogens to males or to postmenopausal women causes an alteration of the serum lipid pattern toward that of the premenopausal woman.<sup>15</sup>

#### *Heparin*

Intravenous heparin has been demonstrated to accelerate the clearing of neutral fat which produces turbidity of the serum in the post-absorptive state. Heparin appears to produce this effect by activating a tissue enzyme lipoprotein lipase. The role of heparin and this enzyme in the intermediary metabolism of cholesterol is not clear.

#### *Other Agents*

Nicotinic acid when administered in extremely large doses has been reported to lower serum cholesterol levels.<sup>16</sup> If further reports confirm this effect, the unpleasant side effects from the large dose required will still limit its clinical usefulness. Plant sterols such as B-sitosterol have been reported to lower serum cholesterol by interfering with its absorption from the gut. Since dietary or exogenous cholesterol appears to be relatively unimportant in human atherosclerosis one is not surprised by the divergent reports that have appeared in the literature concerning its effects.

#### *Therapeutic Application*

If the physician is to employ any of the dietary measures or therapeutic agents thought to alter serum lipids, how is he to select the patients to be treated? Since many patients manifest no clinical evidence of atherosclerosis prior to the moment they are stricken by a fatal "coronary," one would not wish to wait until then. The U. S. Public Health Service has recently completed an extensive study concerning the relative predictive value of serum cholesterol and lipoprotein levels in determining those patients who will later manifest overt atherosclerosis.<sup>17</sup> While most patients who developed coronary atherosclerosis during the study were those with high cholesterol and lipoprotein levels, a significant number occurred in those with low levels. It was concluded that neither determination was of much value in predicting clinical atherosclerosis in the individual case. In general the more economical serum cholesterol determination had the

greater value. Since there is a tendency for serum cholesterol levels to fluctuate widely from time to time in any individual, the average of several determinations would probably have greater predictive value than a single determination. However, it is doubtful that any determination will ever have significant individual predictive value since latent atherosclerosis without clinical manifestations occurs almost universally among adult American males.<sup>18</sup> In fact lipid deposits start forming in the arterial walls during childhood.<sup>19</sup> Consequently, all adult males and post-menopausal females are candidates for the complications of atherosclerosis since most already have the disease, (i. e., individuals vary chiefly in the degree of involvement and the location of their lesions). The patient who dies of a fatal coronary occlusion may have only one-tenth the total atherosclerosis of his neighbor, whose larger and more extensive lesions are primarily in the aorta, do not interfere with blood flow, and produce no symptoms. Since most atheromatous lesions probably develop over a period of many years and there is no adequate way of predicting when the complication of thrombosis will occur, it would seem wise to institute prophylactic measures that may impede the development of atherosclerosis before it is far advanced. Since the disease process is practically universal and there is no satisfactory test to predict who will be stricken, a tentative interim preventive program is proposed for all adult males and post-menopausal females. The program should be modified as new knowledge becomes available. This program can be followed with varying degrees of flexibility. Relatively rigid adherence is proposed for those individuals with overt atherosclerosis, those with a strong familial history of the disease or those with known hypercholesteremia or hyperlipemia. It is possible to follow this program and still enjoy palatable and satisfying meals. There is no evidence that any of the recommendations will be harmful to any patient, nor do they require serious alteration of his way of life. There is presumptive evidence that such a program will decrease the morbidity and mortality from atherosclerosis in the United States.

#### *Proposed Program*

1. Maintain weight at a lean level. Insurance statistics indicate that individuals approximately 10 per cent below "Ideal Weight," have greatest longevity;<sup>20</sup> they also have lowest serum lipid levels.<sup>6</sup> A liberal protein intake is recommended. Daily physical activity is probably desirable.<sup>21</sup>

2. The intake of animal fat and hydrogenated vegetable fats should be kept to a minimum. Fat should be trimmed from meats which should be cooked by broiling, boiling or stewing. Gravies are not recommended. Deep frying even with unsaturated vegetable oils rapidly lowers the iodine number of these oils. The ingestion of fried foods is not encouraged, e. g., boiled or poached eggs are more desirable than when fried or scrambled. Skim milk or buttermilk has most of the vitamins and minerals of whole milk without the animal fat and contains less than half the calories. Corn oil (much cheaper than safflower oil) can be used in the preparation of salad dressing or mayonnaise; with a bit of salt it is a satisfactory

substitute for butter on toast or bread. Most processed cheeses have a high fat content, cottage cheese is an excellent source of protein and is low in fat. Most pastries have a high fat content; angel food cake is an exception which is also a good source of protein. Fruits are excellent forms of fat free desserts. Patients with peptic ulcer will do just as well on a high-protein Sippy mixture made from skim milk, skim milk powder, egg white and flavoring, as on the conventional high fat program. The amphoter action of proteins make them especially effective in neutralizing gastric acidity.

#### *Specific Measures for Individual Patients*

1. Estrogens: Castrate, hysterectomized females should probably receive estrogens at any age. Uterine bleeding is no problem, the increased risk of developing carcinoma is very slight and is far outweighed by the risk of early atherosclerosis. The same is true for the postmenopausal woman who has had her uterus removed. The dose of estrogen required to alter serum lipid levels will usually induce uterine bleeding in the non-hysterectomized postmenopausal woman. The decision to use it in such patients with atherosclerosis must depend on assessing all factors involved. The use of estrogens to decrease serum lipid levels in males with atherosclerosis will be influenced by assessing individual reactions to the feminizing side effects.

2. The use of intermittent heparin to alter serum lipid levels is still considered an experimental procedure. The use of Dicumarol or similar agents for long range anticoagulant effect appears promising for individuals who have sustained myocardial infarction but does not fall within the realm of this discussion.

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## THE ELECTROCARDIOGRAM OF THE MONTH

*The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.*

A 55 year old woman with no known heart disease was admitted to the hospital because of a supraventricular tachycardia. She was given six grains of quinidine sulfate every two hours and when this failed to stop the tachycardia she was digitalized. The quinidine was continued. Her pulse rate then became slower but irregular and the electrocardiogram shown below was recorded at that time.

### *Interpretation*

Lead V<sub>1</sub> (Figure 1) illustrates the problem most clearly. There is a regular auricular rate of 120 per minute. The first two P waves are superimposed upon the preceding T waves; they are conducted by the A-V bundle and the right bundle branch but not by the left bundle branch. The third P wave is not conducted by the A-V bundle; the fourth P wave therefore falls after the A-V bundle has had a long rest period and is conducted normally—the PR interval is short. The

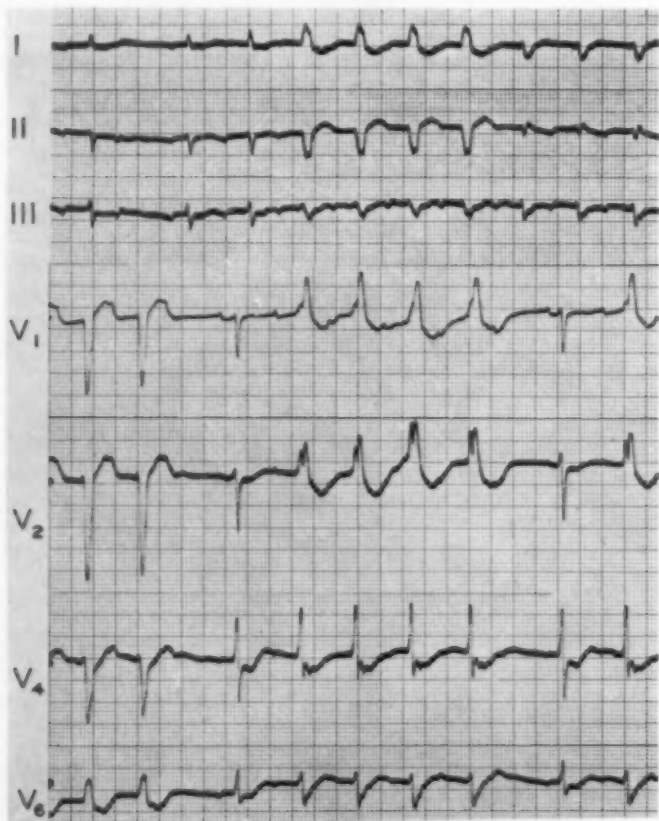


FIGURE 1

fifth, sixth, seventh, and eighth P waves are all conducted by the A-V bundle but the PR interval becomes progressively prolonged; following the ninth P wave the impulse is blocked. The QRS complexes following the fifth through the eighth P waves are of the *right* bundle branch block form. The 10th P wave follows the prolonged rest period offered by blocking of the previous beat and once again normal rapid conduction occurs in the A-V bundle (the PR interval is short).

Thus the tracing shows repeated examples of the block in the right bundle branch, of block in the left bundle branch, and of block in both bundle branches simultaneously (or in the A-V bundle itself). This condition was presumably due to the effects of digitalis and quinidine. When all drugs were discontinued the tracing returned to normal and she has had no further difficulties.

Vectorcardiograms were made (Figure 2) when conduction was normal, when the right bundle branch was blocked, and when the left bundle branch was blocked. The tetrahedron, cube and Frank frames of reference were employed. Two degrees of left bundle branch block were recorded when the horizontal loop of the cube was being examined.

MANUEL GARDBERG, M.D.

IRVING L. ROSEN, M.D.

NEW ORLEANS, LOUISIANA

Cardiac Research Laboratory, Touro Infirmary and the  
Department of Medicine, Louisiana State University  
Medical School.



FIGURE 2

## Editorial

### Soldiers of Peace

During the Middle Ages, Christians and Muslims were locked in a senseless struggle for the possession of a tomb. Millions came from Europe to assault and batter and kill; millions defended and perpetrated destruction in return. In the midst of this, Richard the Lion Hearted of England fell sick. To him came the great Saladin himself disguised as a physician, seeking permission to apply his ministrations. While the henchmen of Richard rattled their sabres and sought for hidden poisons, the King of England himself had no fears. He commanded the doctor to proceed, saying that one whose task was to heal did not distinguish between friend and foe; those who were sworn to give comfort counted no aliens; for them all humanity was one for which all suffering had to be removed.

History stands witness to the fact that doctors through the ages have never known the barriers of nationality, colour or creed in the use of their art. To them all humanity had been one, and they have applied their skill and knowledge to all in an equal degree. The political creed of the medical man which existed from time immemorial is exactly the one towards which the world is now working the hard way—by learning its lessons from the ravages of world wars, by going through endless devastation—that of one humanity, one world.

The Prince of Peace is depicted in religious scriptures as a healer, for peace and healing must go together. None could be a greater champion of peace than Jesus Christ, or a better doctor to Man, working for the greatest degree of comfort not simply for the body but for the soul as well.

What is war? It is nothing but the loosing of the most evil instincts of man, an expression of his destructive genius, which results from the evils of greed, supremacy and possession, and builds for itself a justification. All these, as war itself, are in fact alien to the spirit of a doctor who dedicates himself to the task of reducing suffering.

War seeks to tear the physical being of humanity apart, bruise the body and injure the soul. The doctor forthwith sets his instruments in order and proceeds to repair what has been broken. The struggle of the surgeon in the field camp or the base hospital is not so much to join fractures, set bones, stop bleeding, save life, as it is to struggle against War itself, for fermenting war and its fever are in the last analysis, nothing but a psychosis, an unwholesome state of the mind, an ailment, often artificially engendered. But the doctor does not speak the language of the politician or the philosopher, which is taboo for him, as in the endless dogmatism of the world this language is bound to create more dissension and disrupt peace. He speaks the language of action, he struggles against the ravages of disease and devastation, he builds in the midst

of destruction and his work lives. A doctor is thus a great soldier of peace.

One can well visualise the great good to humanity which can emanate if all these "soldiers of peace" put their heads together, exchange ideas and discuss the results of their significant research. It would definitely make their language of peace universal and understandable at the antipodes.

For some years past, international congresses of medical men under the auspices of the American College of Chest Physicians have been taking place at different points of the globe. They have done tremendous good towards this end; they have not only made it possible for the representatives of one nation to carry back with them the benefits of research in medical science elsewhere, but also have helped underdeveloped nations raise their standards in an effort to be on a par with the more advanced countries. In other words, the congress sessions have marked definite stages in taking the language of peace towards universality.

Healers and doctors have ever played in the past a subsidiary role in the unfolding vistas of history, in which political rivalries and an endless miasma of bloody wars have complicated tremendously the picture of a torn and bleeding world. One can only look with hope to the operation of these forces, wherein medical men play their role in an ever increasing tempo of importance.

*Mohammed Ibrahim, M.D., F.C.C.P.\**

Dacca, East Pakistan

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\*Governor for East Pakistan.

## The President's Page

"On to Tokyo" is our slogan for 1958. Once again, we are given the opportunity to participate in an international congress. In 1950, a large group of our members met in Rome to celebrate the First International Congress on Diseases of the Chest sponsored by the American College of Chest Physicians. During the Second International Congress in 1952, some of the same physicians and their families, with many others, met in Rio de Janeiro to renew the acquaintances which were established in Rome. In 1954, the number of physicians and their families who traveled to Barcelona to celebrate the Third International Congress totalled nearly 2,000 and in 1956, the Fourth International Congress held in Cologne, Germany established a new attendance record of 2,163 physicians and their families representing 58 countries.

For the first time, we will assemble in the Orient and the advance interest expressed by our members indicates that we will have another successful congress. This congress will afford you an opportunity to meet many of your colleagues from various countries and to discuss with them questions of mutual interest.

The Japan Chapter of the College, through its committees and its active Secretary-General, is making plans to see that everyone who attends the congress will have a most enjoyable stay. They are also arranging a splendid program of entertainment in true Oriental style and I can assure you that their hospitality will be something you will always remember. Prime Minister Nobusuke Kishi, the Honorary President of the Congress, and many other Japanese dignitaries will serve as official hosts.

Following the close of the congress in Tokyo, elaborate tours have been arranged which will include visits to many of the beauty spots in Japan, Hong Kong, the Philippines, and Hawaiian Islands. The College chapters in these places are preparing interesting scientific and social programs which I am sure you will not want to miss.

The coming months promise to be busy ones, with nineteen chapter meetings in the United States scheduled between February and May. These chapters meet at the time of the annual meetings of the state medical societies and it is gratifying to note that most of the chapters have begun work on their scientific programs. A one hundred per cent membership attendance should be the goal of every chapter. To accomplish this, the program must be completed in sufficient time to provide adequate publicity and we will appreciate the continued cooperation of chapter officials in this respect. The programs presented at chapter meetings have been of high caliber and several excellent papers given at these scientific sessions have been published in the College journal. The program committees are doing a splendid job in arranging for papers on both cardiac and pulmonary problems. The increase in attendance at our chapter meetings is a compliment to those who have given time and effort to the organization of these programs.

Our chapters provide worthwhile opportunities for members to become familiar with the objectives of the College and many physicians who have participated in chapter work move on to activities at the national level. We are counting on the cooperation of all members in making the 1958 chapter meetings more successful than ever.

We, of course, must not forget our 24th Annual Meeting to be held in San Francisco, June 18-22. Your energetic Program Committee is organizing excellent scientific sessions which I am sure will measure up to the high standards of College meetings. If you plan to attend the Annual Meeting, I would urge you to obtain your hotel reservations immediately. You will find a coupon for obtaining reservations on page xxix of this issue.

*Burgus L. Gordon*



### POST-CONGRESS TOUR

Following the close of the Congress in Tokyo, a group of physicians and their families will travel to Hong Kong where the Hong Kong and China Chapter of the College will present a scientific and social program. It is planned to have a series of Fireside Conferences where the members of the Hong Kong and China Chapter can meet the visiting physicians and discuss scientific projects of mutual interest. This will be followed by the presentation of formal papers by invited guests and members of the chapter and there will be a general discussion of the papers presented. Dr. Li Shu Fan, Regent of the College in Hong Kong, is planning a social program for the physicians and their families.

### COMMITTEE ON NOMINATIONS

Elections for offices which will expire in June, 1958, will be held at the Fairmont Hotel, San Francisco, on Saturday, June 21. Recommendations for elective offices may be addressed to the chairman of the Committee on Nominations, Dr. J. Winthrop Peabody, Sr., 1746 K Street, N. W., Washington, D. C. The other members of the committee are Dr. Sumner S. Cohen, Oak Terrace, Minnesota and Dr. Orin J. Farness, Tucson, Arizona.

### CHAPTER ORGANIZED IN THAILAND



The 69th chapter of the American College of Chest Physicians was organized in Bangkok, Thailand, on October 31, 1957, with 20 charter members. The following officers were elected:

President: Prasert Kangsadal, Dhonburi  
Vice-President: Smarn Muntarbhorn, Bangkok  
Secretary-Treasurer: Sombun Pongaksara, Bangkok

The Governor of the College in Thailand is Dr. Thip Pholpoke, Bangkok. A cocktail party was given in honor of Mr. and Mrs. Murray Kornfeld at the Medical Association Building in Bangkok on Wednesday evening, October 30.

### CHAPTER ORGANIZED IN EAST PAKISTAN

Members of the College in East Pakistan met in Dacca on October 27 to organize the East Pakistan chapter. Speakers on the program were Drs. Mohammed Ibrahim, Governor of the College for East Pakistan, M. A. Mannan, H. Rahman, T. Hossain, and K. A. Khaleque. The following officers were elected:

President: Mohammed Ibrahim, Dacca  
 Vice-President: Hammadur Rahman, Dacca  
 Secretary-Treasurer: Abdul Mannan, Dacca



## College Chapter News

### NEW YORK STATE CHAPTER

The 18th clinical meeting of the New York State Chapter will be held in New York City, February 20-21. The Hotel Commodore will be the headquarters hotel. The following program will be presented:

#### February 20 *Hotel Roosevelt*

Motion Picture Session—Open Heart Surgery

Chairman: Francis O'Donnell, Jr., Buffalo, President, New York State Chapter

8:00 p.m. "Medical Aspects"  
 Irving G. Kroop, Brooklyn

"Surgical Aspects"  
 Philip Crastnopol and Alvin A. Bakst, Brooklyn

#### February 21 *New York Medical College, Metropolitan Hospital Medical Center*

9:00 a.m. "The Formation of a Gastric Tube to By-pass or Replace Obstructing Lesions of the Esophagus"

James M. Winfield and Henry Heimlich, New York City

"Buccal Enzyme Therapy in Acute and Chronic Respiratory Tract Infections"

Irving Innerfield, Harold Shub, and Linn J. Boyd, New York City

"Mucoviscidiosis"

Edward Wasserman and Lawrence Slobody, New York City

"Clinical Application of Tracheal Fenestration"

E. Ernest Rockey, New York City

"Some New Aspects of Experimental Cardiovascular Necrosis"

David Lehr, New York City

"Pneumoconioses in New York State Today"

Morris Kleinfeld, New York City

- 12:15 p.m. Luncheon  
Welcome address: Ralph E. Snyder, Dean, New York Medical College and Flower-Fifth Avenue Hospital; Ferdinand Piazza, Medical Superintendent, Metropolitan Hospital Medical Center, New York City
- 2:00 p.m. Chairman: Emil J. Naclerio, First Vice-President, New York State Chapter, New York City  
"Acute Cor Pulmonale"  
David Scherf, New York City  
"Management of Patients with Angina Pectoris" (Panel)  
Moderator: Linn J. Boyd, New York City  
Panel: Simon Dack, Harry Leinoff, and Samuel A. Thompson, New York City  
"Asthma in Children and its Complications"  
Samuel Untracht, New York City  
"Clinical Indications for Aortography and its Complications"  
Joseph R. Wilder, New York City  
"Cycloserine in the Treatment of Pulmonary Tuberculosis"  
Israel G. Epstein, Brooklyn  
"Steroids in the Treatment of Pulmonary Tuberculosis"  
Paul K. Bornstein, Asbury Park, New Jersey

#### NEW CHAPTER OFFICERS

##### LOUISIANA CHAPTER

- President: Frank W. Pickell, Baton Rouge  
Vice-President: Morton M. Ziskind, New Orleans  
Secretary-Treasurer: Howard A. Buechner, New Orleans (re-elected)

### College News Notes

Dr. Thomas G. Baffes, Skokie, Illinois, has been selected by the U. S. Junior Chamber of Commerce as one of America's Ten Outstanding Young Men of 1957, for his work in developing the first surgical technique of transposition of the great vessels in the hearts of infants.

The following Fellows of the College will present lectures at the Chicago Medical Society's Clinical Conference to be held at the Palmer House, Chicago, March 4-7: Drs. Alvan L. Barach, New York City; Ethan Allan Brown, Boston; George E. Burch, New Orleans, and Richard H. Chamberlain, Philadelphia.

#### CALENDAR OF EVENTS

##### NATIONAL AND INTERNATIONAL MEETINGS

24th Annual Meeting, American College of Chest Physicians  
Fairmont Hotel, San Francisco, June 18-22, 1958

Fifth International Congress on Diseases of the Chest  
Council on International Affairs  
American College of Chest Physicians  
Tokyo, Japan, September 7-11, 1958

##### POSTGRADUATE COURSES

11th Annual Postgraduate Course on Diseases of the Chest  
Warwick Hotel, Philadelphia, March 3-7, 1958

4th Southern Postgraduate Course on Diseases of the Chest  
Grady Memorial Hospital, Atlanta, Georgia, March 10-15, 1958

##### CHAPTER MEETING

Clinical Meeting, New York State Chapter, New York City  
February 20-21, 1958

### ANNUAL MOTION PICTURE PROGRAM

The Committee on Motion Pictures of the College is preparing a program of motion pictures dealing with diseases of the chest to be presented at the 24th Annual Meeting to be held in San Francisco, June 18-22. Physicians who have interesting films are invited to send all pertinent information, i.e., brief description, color or black and white, silent or sound, running time, etc., to the committee for consideration. Please address your letters to: Dr. Paul H. Holinger, Chairman, Committee on Motion Pictures, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

### Book Reviews

**DISEASES OF THE CHEST**, by H. Corwin Hinshaw, M.D., Ph.D. and L. Henry Garland, M.B., B.Ch. W. B. Saunders Company, Philadelphia and London, 1956, \$15.00.

This volume of 727 pages is an excellent presentation of the entire field of diseases of the chest. It is composed of 40 chapters beginning with diagnostic procedure and carrying through all worthwhile treatment and preventive measures. Emphasis is placed on diagnosis as the cornerstone with the numerous special diagnostic procedures now available. Four entire chapters are devoted to diagnosis.

The chapter on "Segmental Anatomy of the Trachea, Bronchial Tree and Lung" emphasizes the importance of such information both in diagnosis and treatment, particularly surgical resection. Measurements of pulmonary function are also given a prominent place.

There are seven chapters, consisting of a total of 130 pages, on various aspects of tuberculosis. Pneumonia, pulmonary fungus infections, tropical pulmonary diseases, and numerous other important conditions are presented. A final excellent chapter is devoted to pulmonary diseases of occupational origin.

Antimicrobial drugs, including chemicals and antibiotics, are presented as they are indicated for various diseases, as well as surgical procedures developed in recent years.

The authors intentionally made the text brief but included reference lists of more recent publications to aid those who desire to do additional reading. The volume is profusely illustrated and contains a good index.

This book is highly recommended to physicians everywhere.

J. Arthur Myers, M.D.

**LYMPHATICS, LYMPH AND LYMPHOID TISSUE**, by J. M. Yoffey, M.D. and F. C. Courtice, M.D. Harvard University Press, Cambridge, Massachusetts, 1956, 510 pages, \$10.00.

The subjects presented in this volume have an important bearing on clinical medicine in the daily practice of those specializing in diseases of the chest. The text contains an amazing collection of basic information supported by extensive research studies carried out by the authors. Also, it carries critically chosen, well-coordinated cardinal data derived from pertinent investigations of others. The material offered reflects the thoroughness and competence with which the authors approached their problem. Controversial and unsolved problems are considered with impartial objectivity. Illucidating tables, graphs, diagrams and pictorial illustrations are plentiful and greatly enhance the instructive value of the book. References at the end of chapters are well selected and may serve as useful guides for further orientation. Discussion of the experimental and clinical application of radioactive isotopes, the inclusion of items, such as pulmonary edema, pleural effusion, the detailed portrayal of physiologic pulmonary catharsis, the description of potential routes of lymphogenous spread of infections deserve special mention. Due attention is paid to pathways leading to sites of the Troisier-Virchow sentinel nodes. Ample space is devoted to the discussion of the clinical significance of lymphocytes.

This book is characterized by the ideal attributes of fundamental contributions to the intelligent and prudent practice of medicine; therefore, it is highly recommended to all concerned.

Andrew L. Banyai, M.D.

## MEDICAL SERVICE BUREAU

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**Staff physician** wanted immediately for newly constructed 77-bed tuberculosis hospital, operated by Ohio Department of Health. Experience in pulmonary diseases desired, but not essential. Ohio license or eligibility for same required. Beginning salary \$10,320, with yearly increases. Liberal vacation, sick leave, and retirement benefits. Furnished two-bedroom apartment available at nominal rent. Apply: Harold H. Cashman, M.D., Director, Southeast Ohio Tuberculosis Hospital, Nelsonville, Ohio.

**Staff physician** wanted for 600-bed, modern tuberculosis hospital. Medical license or eligibility required. Hospital located in college town, 30,000. Active outpatient department. Suspected cases admitted for diagnosis. Vacation, sick leave, retirement and social security. Salary \$9360 up, depending upon qualifications. Apply: Medical Director, Eastern North Carolina Sanatorium, Wilson, North Carolina.

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**Full-time physician** wanted for new 440-bed tuberculosis division of large general hospital in the east. Associated with two medical schools for teaching purposes, with opportunity for research. Complete surgical and pathological facilities. Please address inquiries to Box 295A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

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**Associate Member**, American College of Chest Physicians, age 40, lung specialist from Paris, former director of chest hospital in Middle East, consultant physician at chest hospital and on faculty of medicine in Southeast Asia, clinical experience, seeks position in chest hospital. Please address inquiries to Box 956, Stanford University, Stanford, California.



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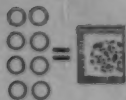
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